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BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 1 1960

DEMETHYLCHLORTETRACYCLINE

BY

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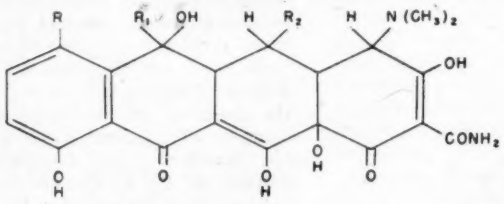
A newly discovered antibiotic may either be entirely new or prove to be related in structure and action to another already known. However close a relationship, the discovery may have been worth while if the new member of what may already be a group possesses advantages over the rest in antibacterial activity, pharmacological behaviour, or other properties.

Such a group is that of the tetracyclines, the prototype of which was "aureomycin,"[1] introduced in 1948, followed by "terramycin"[2] two years later. Determination of their chemical structure (Fig. 1) showed that



	R	R_1 =	R_2 =
TETRACYCLINE	H	CH_3	H
CHLORTETRACYCLINE	Cl	CH_3	H
OXYTETRACYCLINE	H	CH_3	OH
DEMETHYLCHLORTETRACYCLINE	Cl	H	H

FIG. 1.—Chemical structure of four tetracycline antibiotics.

these antibiotics differed only in possessing respectively an added chlorine atom and an OH group. A third member of the group, tetracycline,[3 11] was then obtained, possessing neither of these attachments. There were thus aureomycin (chlortetracycline), terramycin (oxytetracycline), and tetracycline[4] ("achromycin," "tetracyn"), which are here referred to as CTC, OTC, and TC.

Differences Between the Older Tetracyclines

It is not to be expected that such closely related substances should differ greatly in any property. Their antibacterial "spectrums" are closely similar, though CTC is usually more active against staphylococci and pneumococci, OTC against *Pseudomonas pyocyanea*, and TC against *Proteus*.[13 17] Cross-resistance between them is complete, whether in organisms resistant when isolated[14] or in those artificially habituated.[15] The discovery of TC was welcomed on other grounds than these. TC produced higher and better-sustained levels of antibiotic activity in the blood than OTC[16] and more particularly than CTC, the exceptional instability of which explains this difference. Moreover, TC was found less apt to produce gastro-intestinal side-effects, notably the acute enterocolitis caused by resistant staphylococci, which had proved to be so dangerous a complication of therapy with CTC and particularly OTC.[5-8]

In a study at the Boston City Hospital,[9] OTC was observed to produce diarrhoea of greater severity and about twice as frequently as CTC. *Staphylococcus aureus* was the only or the predominant organism in the faeces of 27 of the 38 patients with diarrhoea accompanying OTC treatment, but in only 4 of 22 receiving CTC. It had been shown previously that staphylococci were more often resistant to OTC and to a higher degree than to CTC.[10] In a continuation of this study,[12] diarrhoea was found to be much less frequently produced by TC. On the other hand, in a series of 288 cases of pneumonia treated with tetracyclines at St. Bartholomew's Hospital[17] and studied retrospectively by simple summation and averaging of charted bowel actions, it did not appear that there was any significant difference between the amounts of diarrhoea (which was rarely severe) produced by the three drugs. Mainly because of its reputation for being better tolerated the clinical use of TC has largely replaced that of CTC and OTC in recent years.

Properties of Demethylchlortetracycline

In 1957 McCormick *et al.*[18] described a new family of tetracyclines characterized by the absence of a CH_3 group which is found in all others. One of these, demethylchlortetracycline (DMCT) was produced by a mutant of Duggar's original strain of *Streptomyces aureofaciens*, from which CTC had first been obtained. The structure of DMCT is shown in Fig. 1. Its first exceptional property to be demonstrated was a very high degree of resistance to degradation by acid or alkali, and, as will be seen, this stability is a valuable advantage. Its antibacterial activity compared favourably with that

*Aided, in part, by a grant (to M.F.) from the National Institutes of Health, U.S. Public Health Service.

of other tetracyclines. Thirdly, it was found first in dogs, and later in a series of studies in man,[19 20 21] to remain in effective concentration in the blood longer than any other tetracycline. These properties naturally excited much interest, and many further studies of DMCT have been undertaken, the results of 15 of which were presented at the Symposium on Antibiotics in Washington, November 4–6, 1959: 16 further papers on the subject were only "read by title" on this occasion. The text of most of these papers and the findings of other work yet to be published have been made available to us, and the following is a digest of this new information* together with observations of our own.

Antibacterial Action of DMCT in vitro

Reports by 13 different groups of workers, 10 of which have been published,[17 22–30] deal with the susceptibility to DMCT of 3,227 strains of important pathogenic species. A dilution method with twofold differences was used in most of these studies, and comparison was made with TC; often also with OTC and CTC. The almost universal finding was that DMCT was more active than TC by a factor of 2, or of equal activity, but rarely of less. This applies both to Gram-positive organisms and to Gram-negative, the latter including many derived from infections of the urinary tract,[25 26] and to species of *Salmonella* and *Shigella*.[23 29] The more accurate turbidimetric method used by Dornbush and Pelcak[27] showed the factor by which the activity of DMCT exceeded that of TC to vary from 1.1 to 4.8 for different strains of various species, the average being 2.3 for *Streptococcus pyogenes* and about 2.0 for most other organisms. This is the general trend of the findings, but some exceptions were found in a study of 861 strains by Hirsch and Finland,[22] including a lesser relative activity of DMCT against resistant strains of staphylococci.

Against normally sensitive staphylococci CTC is recognized to be more active than TC, and comparison of DMCT with CTC against this organism shows equivalent activity. Garrod and Waterworth[17] compared their bactericidal action and found almost identical initial rates of kill, but as CTC underwent degradation the curve flattened and growth followed, whereas the action of DMCT proceeded to extinction. DMCT may therefore be regarded as CTC with the added virtue of stability.

Absorption, Distribution, and Excretion

Originally demonstrated in dogs by Kanegis and Dearborn, and since confirmed in rabbits by Knothe,[28] the higher sustained levels attained by DMCT in the blood have been shown also to occur in man by three principal studies —those of Sweeney *et al.*,[19] Kunin and Finland,[20] and Hirsch and Finland.[21] The method used was to administer single, or in some experiments repeated, oral doses of DMCT and other tetracyclines to normal subjects in cross-over studies, and to assay the antibiotic in the blood at intervals after a dose, either by the *Bacillus cereus* cup-plate method or by a tube-dilution method using this organism or a staphylococcus, or a haemolytic streptococcus. Results have been expressed in two ways: (1) as w/v—that is, μg./ml. concentrations of the antibiotic in the blood, and (2) as tetracycline equivalents—that is, in terms of the degree of antibacterial activity against the test organisms —thus taking into account not only the concentration attained but the intrinsic activity of each form of tetracycline.

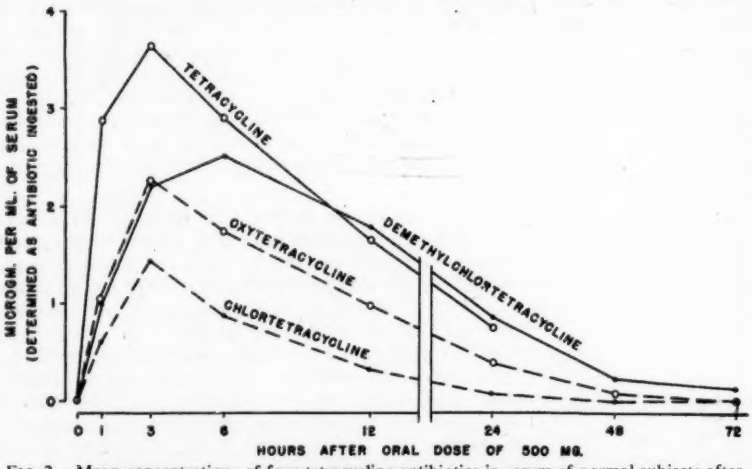


FIG. 2.—Mean concentrations of four tetracycline antibiotics in serum of normal subjects after single oral doses of 500 mg. equivalents of their hydrochlorides (after Kunin and Finland[20] and Hirsch and Finland[21]). Concentrations expressed as weight of administered antibiotic.

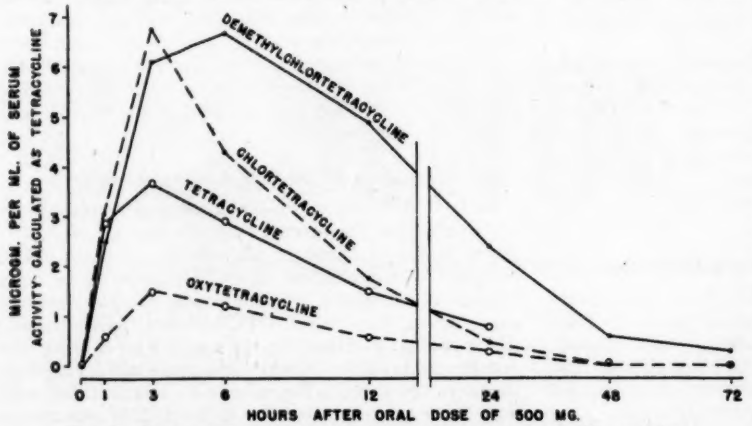


FIG. 3.—Same as Fig. 2. Concentrations calculated as tetracycline activity.

The findings in a series of such tests[20 21] are expressed in these two ways in Figs. 2 and 3. In terms of w/v concentrations (Fig. 2) TC attains the highest levels in the first few hours. DMCT reaches its peak concentration more slowly, and its level declines more gradually,

*Only those papers are actually cited here which either have been published or are known to be in press.

so that after about the tenth hour it exceeds that of TC as well as of OTC and CTC, which are lower throughout. This decline is so slow that DMCT is still detectable in the serum after 48 and even 72 hours. When the same results are expressed in terms of tetracycline activity* (Fig. 3) the superiority of DMCT is even more evident, its activity in the blood greatly exceeding that of all three other tetracyclines from the third hour onwards. It was shown[20] at an early stage that the rate of renal clearance of DMCT is only 43% of that of TC, a fact which evidently accounts for its long persistence in therapeutic concentrations in the blood. In these experiments the capsules of tetracyclines other than DMCT contained citric acid or glucosamine hydrochloride to promote better absorption: DMCT itself is not affected by such additions. Further studies[29 31 34] on similar lines, either in normal subjects or in patients undergoing treatment, have yielded generally comparable results, although Perry *et al.*[24] observed consistently lower levels of antistreptococcal activity in serum from 0.3 g. of DMCT than from 0.5 g. of TC; these various findings include confirmation that DMCT (in a liquid formulation) produces good blood levels in children,[36] and observations on urinary excretion: as is to be expected, DMCT appears in the urine later than TC and in lower concentrations.[37]

Detailed studies of distribution and excretion after single intravenous 500-mg. doses (of DMCT also 250 mg.) have been made by Kunin, Dornbush, and Finland.[33] The curves of blood concentrations after administration by this route are shown in Fig. 4. Among the contrasting properties of the four tetracyclines revealed in this study (for data see Table) are the slow renal excretion and consequently much longer "half-life" of DMCT, the rapid removal of CTC by non-renal mechanisms—that is, degradation — and the rapid renal clearance of OTC, of which the greatest percentage of the dose is excreted in the urine. All four were distributed through a relative volume greater than that of the body weight, indicating sequestration in some tissues. In another study Kunin and Finland[34] showed that the concentration of DMCT in bile may be 20–32 times higher than in the serum 7–24 hours after an intravenous dose: like other tetracyclines, it is thus sequestered in the liver. In separate dialysis equilibrium studies,[33] the percentages bound to plasma were found to be TC 24, OTC 20, CTC 47, and DMCT 41.

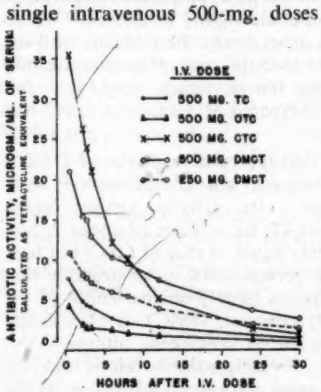


FIG. 4.—Average concentrations of antibiotic in serum of same four normal subjects after intravenous injection of each of the tetracycline antibiotics. Concentrations calculated as tetracycline equivalents. (From Kunin, Dornbush, and Finland.[33])

Penetration into other body fluids.—Boger and Gavin[35] gave single doses of 0.5 or 1 g. of DMCT to 32 patients with uninflamed meninges, and found low levels (1/20 to 1/50 of those in the serum) in cerebrospinal fluid obtained 4–12 hours later. In two other similar studies,[30 37] on only five and two patients respectively, no activity was detected in any specimen of cerebrospinal fluid. One of these papers[30] also records that concentrations equal to those in the serum were found in synovial fluid from two patients undergoing treatment with DMCT.

Distribution and Elimination of Four Tetracycline Homologues After Intravenous Injection in Four Normal Young Men (From Kunin, Dornbush, and Finland[33])*

Rates	TC	OTC	CTC	DMCT	$DMCT_{250}$
Decay in serum (%/hr.)	8·2	7·6	12·4	5·5	6·0
Half-life in serum (hours)	8·5	9·2	5·6	12·7	11·8
Relative volume distribution (% of body weight)	159	189	148	179	148
Clearance from serum (ml./min.)	149	162	205	112	99
Renal clearance† (ml./min./1·73 M^2)	74	99	32	35	35
Ratio: Clearance of antibiotic / Clearance of creatinine	62	85	30	27	32
% of dose excreted in 96 hours	60	70	18	39	43
Removal by renal mechanisms (%/hr.)	4·9	4·4	2·9	2·1	2·6
Time required to remove 50% of dose by renal mechanisms (hours)	14·1	16·0	25·9	35·5	27·2
Removal by non-renal mechanisms (%/hr.)	3·3	3·2	9·5	3·4	4·0
Time required to remove 50% of dose by non-renal mechanisms (hours)	21·7	24·0	7·3	20·1	19·1

* Average values after single doses of 500 mg. of each and also 250 mg. of DMCT (designated $DMCT_{250}$); average weight of subjects was 67·8 kg.
† There was no relation to rate of urine flow between 2 and 14 ml. /min.

Excretion in faeces.—In a cross-over study in 48 subjects reported by Garrod and Waterworth,[17] in which the effects of 600 mg. of DMCT and 1 g. of TC daily for five days were compared, assays of the antibiotic content of faeces showed them to contain an average of 339 (range <60–600) μg./g. of DMCT and 1,196 (range 30–3,500) μg./g. of TC. This suggests that DMCT was better absorbed than TC. That the drug in the faeces is largely unabsorbed and not present owing to biliary excretion was suggested by the finding of little or no antibiotic in the faeces of subjects given TC intramuscularly. Observations by Sweeney, Dornbush, and Hardy[38] show considerable individual variation in the absorption of DMCT, which probably applies to all tetracyclines. About 5% of individuals regularly absorb these drugs poorly, the amount in the faeces then varying inversely with serum levels and with the amount recoverable in the urine.

Effect on Experimental Infections

Kuck and Redin[32] compared the therapeutic activity of TC and DMCT in several mouse infections. When the drug was added to the diet DMCT was nearly twice as effective against a staphylococcal infection, not only with respect to the plasma concentration required for equal therapeutic effects, but in terms of the oral dose needed to maintain the therapeutic plasma level. Against infections with *Str. pyogenes* or pneumococcus, approximately equal plasma concentrations and equal doses were required for comparable effects. Against a *Klebsiella pneumoniae* infection, DMCT and TC were equally active with respect to the plasma concentrations required for therapeutic effect, but twice as much TC was required to achieve the higher plasma levels needed to control this infection. In several series of tests of the effect of single subcutaneous doses DMCT was usually superior, evidently owing mainly to its more prolonged action: that it gives more persistent plasma levels in mice as in other animal species was verified.

*This activity is measured against *B. cereus*. The factors by which the activity of DMCT exceeded that of TC against the three organisms used in these assays were *B. cereus* 3.1, *Str. pyogenes* 2.2, and *Staph. aureus* 1.5.

Clinical Results

Clinical reports with varying amounts of detail are available about the effect of DMCT in pneumonias,[24 39] infections of the urinary tract,[25 31] brucellosis,[42] genital infections,[40] pustular dermatoses,[43] and amoebiasis[41]; others unpublished refer to surgical infections. Results have also been reported in a wide variety of medical diseases for which tetracyclines have been used in the past (Lichter *et al.*,[44] Fujii *et al.*,[37] Finland *et al.*[45]): the two last-named papers include results obtained at the same time with TC in similar cases. The numbers of patients varied from 9 to 169, and they were treated for periods varying from one day to several weeks with daily doses of 0.5–2 g. and individual doses of 125 mg.–1 g., sometimes with a larger initial loading dose.

With one exception, that of Elsdon-Dew *et al.*,[41] who got poorer results in amoebiasis than with other tetracyclines, these reports conclude that DMCT is as effective as TC and other tetracyclines in the whole range of infections for which these drugs have been used, but it has also been found in most of these studies that a smaller dose of DMCT has an equivalent effect. It is difficult to make a significant comparison between two such similar drugs, and the conclusion just stated may not be adequately based on any single one of these studies, but a consensus of opinion tallying with what is to be expected from the ascertainable properties of DMCT may be accepted with some assurance.

Untoward Effects

The tetracyclines have no serious toxicity unless given in excessive doses, and DMCT appears to be no exception. Its liability to cause diarrhoea is slight if moderate doses are given: whether it is greater than that of the other tetracyclines from larger doses only further experience can finally decide. Perry *et al.*[24] saw no untoward effects in 18 patients given 300 mg. twice daily, but nausea or vomiting occurred in 11 (38%) out of 29 patients given this dose four times a day. Lichter *et al.*[44] observed such disturbance in 2 out of 126 patients given up to 600 mg. daily, in 3 out of 12 given 1 g., and in 11 out of 18 given 2 g. Finland *et al.*,[45] in a simultaneous comparison, found that when DMCT was given in 50–60% of the dose of TC, the latter caused rather more gastro-intestinal side-effects. Garrod and Waterworth,[17] in a cross-over study in 48 normal subjects given 600 mg. of DMCT and 1 g. of TC, observed equal frequencies and degrees of mild disturbance in both groups (average 1.4 bowel actions daily in each).

An exaggerated sunburn reaction in patients being given DMCT has been recorded. In a case described by Morris[46] from the seaside resort of Corpus Christi, Texas, exposure to bright sunlight on the fifth day of treatment with 600 mg. of DMCT daily caused severe sunburn of exposed surfaces, with high fever, eosinophilia, and increased blood platelets. Deliberate attempts to reproduce this effect, about which we have had personal communications, were successful in Philadelphia in September and in Oklahoma in October: similar experiments with TC gave negative results. Four further instances are reported by Falk[47] among 27 ambulatory patients treated in Reno, Nevada. Carey[48] reports that only 40 patients among 2,682 treated with DMCT have exhibited this phototoxic reaction or anything which resembled it. It occurs only on skin exposed to sunlight containing rays in the range 2,700–3,200 Å: these are filtered out by ordinary window glass, and exist in the sunlight of temperate zones only in the summer. The reaction is not one of hypersensitivity, but a true phototoxicity, an important distinction as recently noted by Harber *et al.*[49] in connexion with a similar reaction to chlorothiazide.

Discussion

The tetracyclines have the broadest spectrum of all the antibiotics, ranging from the rickettsias and such viruses as are susceptible to chemotherapy through all the pyogenic cocci to the majority of the various Gram-negative bacilli, including the intestinal group and such others as *Brucella* and *Haemophilus*. There are many infections of the air passages, alimentary tract, urinary tract, and skin in which their use is appropriate, particularly if the bacterial cause has been identified and its sensitivity to the antibiotic verified.

We are concerned here with the relative merits of a group now including four substances. A natural first reaction must be one of astonishment that a change involving only one, two, or four atoms in a large molecule should have such a variety of effects on pharmacological behaviour and on antibacterial activity. There is a long way to go in relating structure with biological activity before the effects of these small changes can be explained. Nevertheless they are facts; a discriminating physician aware of them can choose a tetracycline for a specific purpose, and there are purposes for which each of them could rightly be chosen. We do not suggest that this is often done: the position until the advent of DMCT was that TC was preferred because it is better tolerated, and few physicians would have felt themselves seriously hampered if CTC and OTC had ceased to be obtainable.

We do not suggest that the relative merits of DMCT can yet be finally assessed, but it has several well-ascertained advantages. Its activity against many bacteria exceeds that of TC by a factor of about 2, and is perhaps approximately equal to that of CTC, but here comparison is difficult because CTC is so unstable that the result of a test depends largely on the length of the incubation period. By contrast, DMCT is exceedingly stable. It is perhaps better absorbed, although this requires further proof. What is quite certain is that it is much more slowly excreted, with the result that after the first few hours, during which its level in the blood is below that of TC although higher than that of OTC or CTC, it sustains an adequate level in the blood for much longer than any of the other three. This statement refers to actual concentrations: in terms of activity against many bacteria its superiority is even more striking.

Two conclusions are justified by these facts. It may confidently be said of DMCT that only two daily doses are required: the elimination of any need for six-hourly schedules of administration is an important advantage for patients who need, among other things, sleep. Out-patients are also less likely to miss a dose if it is to be taken only before breakfast and supper. Secondly, owing also to its greater antibacterial activity DMCT gives an equivalent therapeutic effect from a smaller dose than TC. Alternatively, an equal dose of DMCT is more likely to achieve the desired effect. These are very solid advantages, and, unless there are drawbacks of equal weight to set against them, DMCT may prove to be the preferred tetracycline of the future.

One drawback, certainly not of much consequence in ordinary circumstances, is the phototoxic reaction already described. The only other which has come to light, the importance of which has not yet been

measured, is the gastro-intestinal disturbance produced by larger doses. How far, if at all, this exceeds that produced by TC remains to be determined by further experience. This kind of tetracycline diarrhoea—as distinct from the much severer form due to infection of the gut by resistant staphylococci—deserves further investigation, and if some means could be found of overcoming it without interfering with the absorption of the drug all tetracycline therapy would be facilitated. Is it a chemical effect on the bowel mucosa or on the bowel contents, or does it operate through disturbance of the balance of the intestinal flora? Is it promoted by relatively poor absorption and thus a higher concentration of the drug in the bowel? If answers could be found to these questions, this nuisance factor might cease to operate in the choice between one tetracycline and another, or between tetracyclines generally and other drugs.

Summary

This paper reviews all the existing literature on demethylchlortetracycline (DMCT) and the results of other unpublished studies.

The significant properties of DMCT are: (1) high stability; (2) an activity against most bacteria exceeding that of tetracycline (TC) by approximately twofold; and (3) a rate of renal excretion less than half that of TC, with the result that therapeutic concentrations are maintained in the blood for a much longer time after a dose.

It may be concluded from these facts that DMCT can be administered at longer intervals than other tetracyclines—two daily doses should suffice; and that a smaller dose of DMCT than of TC should achieve an equivalent therapeutic effect.

Larger doses of DMCT are apt to cause diarrhoea: whether this liability exceeds that of TC is not certain.

A phototoxic reaction peculiar to DMCT may occur in treated patients exposed to bright sunlight.

We are indebted to Lederle Laboratories Ltd. for the supplies of DMCT ("declomycin," "ledermycin") used in our own studies.

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STEATORRHOEA IN THE ADULT*

BY

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In this lecture I propose to survey the causes of steatorrhoea, and to consider the differential diagnosis and treatment of the malabsorption syndromes.

The pathogenesis of steatorrhoea is a very large subject and the number of conditions that can give rise to it is formidable. For this reason I shall deal with them in tabulated form and select from the list, for closer scrutiny, the subjects in which recent advances have been made, or on which further work is needed.

Group 1

Coeliac Disease. Idiopathic Steatorrhoea. Tropical Sprue

Until a short time ago the only justification for grouping these three together was that the cause of each was unknown.

It is possible, as Adlersberg (1957) believes, that all are due to a constitutional genetic defect which is unmasked by a number of different trigger mechanisms. In the case of coeliac disease and idiopathic steatorrhoea at least, the evidence for a common genetic background is quite strong. Cooke, Peeney, and Hawkins (1953) noted that many of their adult patients seemed to conform to a particular somatic type. Other workers, who

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were careful to exclude cases of pancreatic failure, showed that diarrhoea and intolerance of fats were more common among relatives of patients with coeliac disease than in control families (Boyer and Andersen, 1956), and that coeliac children were born to older mothers and in later child ranks than was likely to be due to chance (Thompson, 1951). Moreover, there is a significant increase in the incidence of blood group O among patients with idiopathic steatorrhoea, and both idiopathic steatorrhoea and coeliac disease occur quite often in more than one member of a family (Joske and Benson, 1958; Carter, Sheldon, and Walker, 1959). This happened three times in my series, and in one of these families one member had tropical sprue and the other idiopathic steatorrhoea.

Further evidence linking coeliac disease with idiopathic steatorrhoea is provided, firstly, by the fact that in many adult cases the disease begins in childhood; secondly, by the response to treatment with the gluten-free diet; and, thirdly, by the observation that the histological lesion in the small intestine is probably identical in the two diseases.

The exact way in which wheat and rye gluten cause symptoms in patients with the gluten-enteropathy remains unknown. Gluten added to the diet not only increases the amount of dietary fat excreted but also increases the amount lost from endogenous sources. Weijers and van de Kamer have shown that feeding gluten or gliadin raises the bound forms of glutamine in the blood to higher levels in children with coeliac disease than it does in normal controls. They also showed that if the gluten is totally hydrolysed to its component amino-acids it is harmless and that free glutamine by itself is non-toxic. They concluded that the harmful fraction is a glutamine-peptide complex (van de Kamer and Weijers, 1955; Weijers and van de Kamer, 1955).

Frazer (1956) has been unable to demonstrate any difference *in vitro* between the digestion of wheat gluten by juices obtained from children with coeliac disease and from normal subjects, but the product of such digestion, although harmless to normal individuals, is toxic to patients with coeliac disease. He has shown, further, that if the toxic fraction is incubated with an extract of pig's intestinal mucosa it loses its toxic properties. In recent experiments he and his colleagues have demonstrated that the harmful effect is not due to the chemical treatment that the flour has received or to residual gluten still present in the enzymic hydrolysate. As a result of their studies, they have suggested that the basic defect in the gluten enteropathy is the absence of an enzyme from the wall of the intestine, lack of which makes it impossible for a patient with the coeliac syndrome to break down glutamine containing peptides (Frazer, Fletcher, Ross, Shaw, Sammons, and Schneider, 1959). Such a mechanism would explain the high levels of bound glutamine in the blood in patients with the coeliac syndrome; but, curiously, it is the glutamine in the form in which it is bound in wheat and rye protein which does the damage, for it occurs in considerable quantities in bound forms in other proteins, such as casein, and yet these are harmless.

In spite of these interesting experiments, and until the aetiology is precisely known, we should be wary of assuming that idiopathic steatorrhoea and coeliac disease are one and the same. Some, probably the great majority, of the adult cases are due to a gluten-induced enteropathy, but there remains a small number that do not respond to the gluten-free diet, and yet no other cause for the steatorrhoea can be found. It is tempting to assume that these patients have not adhered to their diet strictly; but French, Hawkins, and Smith (1957), in their careful study of 22 patients, found six who failed to improve, and they were unwilling to accept that breaks in the dietary regime were always responsible. It is possible that in these patients the disease had progressed too far for recovery to take place, but it is also possible that they represent a separate entity with a different aetiology. In future, careful correlation between the response to treatment and the histology and perhaps the histochemistry of the small intestine may provide the answer.

It is clear that tropical sprue differs from idiopathic steatorrhoea, for it will not respond to the withdrawal of gluten from the diet, but it will to treatment with antibiotics. The results obtained by French, Gaddie, and Smith (1956) were so definite that I have been surprised that they have not been confirmed by other workers in India or the Far East with access to larger series of cases; but perhaps our dwindling political and medical contact with the sprue areas is the cause of this. In view of the different therapeutic response, it is odd that the histological picture of the small intestine in tropical sprue is so similar to that in idiopathic steatorrhoea and coeliac disease. This could be used as an argument in support of Adlersberg's idea of a common genetic background, but it may be that the atrophy of the mucosa and the loss of villous pattern can result from a number of different causes and need not imply a common aetiology.

Group 2.—Failure of Digestion of Fat

Obstructive Jaundice. Disease of the Pancreas (Alcoholic Cirrhosis). Gastric Operations

In this group the steatorrhoea is primarily the result of impaired fat-digestion. I have linked alcoholic cirrhosis with the pancreatic steatorrhoeas because here the failure of fat-absorption is due to pancreatic damage and not to the primary liver disease (Fast, Wolfe, Stormont, and Davidson, 1959). Traditionally, the steatorrhoea in this group has been regarded as a nuisance which causes considerable loss of weight, but it has not been thought to be of any real significance. This idea is both false and dangerous. It is true that, at least in the first two, anaemia does not usually occur and water-soluble substances are absorbed normally, but in all three loss of fat-soluble vitamins in the stools may lead to serious symptoms.

Fig. 1 shows the pelvis and right hip of a patient who developed steatorrhoea after a by-pass operation on her stomach. Her serum calcium was low and biopsy of the bone revealed osteomalacia. The bones were so soft that the pin used to fix the fracture protruded right through the neck of the femur.

Interest in the role of the pancreas in the malabsorption syndromes has been reawakened as the result of recent work on fibrocystic disease. Originally it was thought to be solely a disease of the pancreas, but it is now known to be a widespread disorder of exocrine glands involving as well as the respiratory tract the liver, Brunner's glands in the intestine, and the sweat and salivary glands (Di Sant'Agnese, 1956). It is hereditary and is transmitted as a recessive. Several theories have been put forward to explain its manifestations, the most ingenious being that, as all the affected glands are cholinergic, the symptoms might be the result of their continued over-

secretion due either to liberation of excessive quantities of acetylcholine or lack of the enzymes which destroy it (Roberts, 1959).

Fibrocystic disease comes within my terms of reference because, although it is an important cause of death in childhood, the sufferers may survive into adult life. The involvement of the pancreas is clinically silent and painless, and the true cause of the defect in secretion is easy to overlook. Some of the patients have bronchiectasis and emphysema, others cirrhosis of the liver, and it has been recorded in association with transposition of the viscera and Kartagener's syndrome. After childhood the pathology of the pancreas is a lipomatosis, and the pathognomonic cystic fibrosis is seen only in infancy (Andersen, 1958; Brown and Smith, 1959).

Yet another syndrome which has recently come to the fore is the triad of non-insulin-secreting islet-cell tumours of the pancreas, marked gastric hypersecretion, and recurrent ulceration of the stomach and small bowel, first described by Zollinger and Ellison (1955). In many of the cases the tumours are multiple and involve other endocrine glands, including the pituitary, parathyroids, and adrenals, in addition to the pancreas.

The main emphasis in the first papers was on the severity of the gastro-intestinal ulceration, but Maynard and Point (1958) drew attention to a patient in whom the gastric hypersecretion was accompanied by malabsorption and steatorrhoea. The cause of the steatorrhoea is believed to be due either to inactivation of pancreatic enzymes at the low *p*H induced by the overwhelming flow of acid, or to an outpouring of mucus by the

FIG. 1.—Pelvis and right hip of patient with osteomalacia after a by-pass operation on the stomach.

intestine in response to this. Whichever is correct, England, French, Rawson, and Stammers (1960) have shown that if the pancreatic tumour can be totally removed the secretion of acid falls to normal and the steatorrhoea disappears. However, Zollinger and Elliott (1959) believe that the safest course is to carry out a total gastrectomy and remove the acid-secreting mucosa completely, because if metastasis of the tumour has occurred the hypersecretion of acid will continue from any gastric mucosa that remains.

The steatorrhoea that follows partial and total gastrectomy is also chiefly the result of faulty digestion, and it has two main causes. The first is that in total gastrectomy, in Polya partial gastrectomy, and in by-passed stomachs the food does not enter the duodenum, and thus the natural stimulus for the secretion of pancreatic juice and the release of bile into the intestine is lacking. The second is that in all gastric resections, including Billroth's first operation, the gastric reservoir is reduced and food is shot into the upper small intestine too rapidly for adequate mixing (Brain, 1953; Main and Gobbel, 1960). In these patients meals rich in carbohydrate make the steatorrhoea worse, possibly by promoting the reflex secretion of adrenaline which inhibits the flow of pancreatic juice. Sometimes the steatorrhoea can be decreased by giving pancreatin or bile salts by mouth, but in adequate doses they are likely to make the diarrhoea worse. However, Vanamee, Lawrence, Levin, Peterson, and Randall (1959) have shown that as little as an ounce (28 ml.) of N/10 HCl given before meals will reduce the steatorrhoea and stop the diarrhoea by providing the physiological stimulus for the secretion of pancreatic juice. Presumably this is the explanation for the old clinical observation that very small doses of acid will exert a dramatic effect on the diarrhoea of achlorhydric patients.

A third mechanism which may cause steatorrhoea in some of these patients in whom gastro-duodenal continuity has not been preserved is dilatation of the afferent loop and stagnation of its contents. It has been shown that when this occurs coliform organisms can be cultured from the dilated bowel and the steatorrhoea can be decreased by antibiotics (Wirts, Goldstein, Calaresu, Kramer, and Concannon, 1959).

Group 3.—Derangement of Normal Anatomy Alteration in Bacterial Flora of Gut

Blind Loops. Fistulae. Diverticulosis of Jejunum. Resections

In Oxford we have always been interested in this group, which traditionally is closely bound up with the pathogenesis of the megaloblastic anaemias.

Most of the earlier reports were concerned with the ill effects of strictures of the small intestine or with the results of anastomoses which had isolated loops of gut and shortened the effective length of the bowel. Recently we have learnt that similar symptoms may be produced by massive diverticulosis of the small intestine.

In 1930 Taylor reported the case of a patient with pernicious anaemia and a gastro-enterostomy in whom numerous diverticula of the jejunum were found at necropsy. Montuschi (1949) and Zingg (1950) each described cases of jejunal diverticulosis with steatorrhoea, and in 1954 Bedford and I were lucky enough to encounter two patients with the triad of jejunal diverticulosis, steatorrhoea, and megaloblastic anaemia (Badenoch and Bedford, 1954). It occurred to us that the narrow-mouthed diverticula might be acting as stagnant pools where bacteria could flourish, and that the condition could well be regarded as a variant of the blind-loop syndrome.

The classical views of Faber (1895) and Meulengracht (1921), that the anaemia and disturbance in intestinal function which occur in these patients are the result of bacterial invasion of the bowel, have been amply confirmed. Experiments on animals have shown that if strictures are made in the upper intestine the incidence of anaemia is greater if the bowel becomes infected (Seyderhelm, Lehmann, and Wichels, 1924), and, as Cameron, Watson, and Witts (1949) have demonstrated, blind loops more often give rise to anaemia and steatorrhoea if they are designed so that normal peristalsis

cannot empty them and they become dilated with stagnant contents.

In the human cases, studies of the absorption of vitamin B_{12} have also emphasized the importance of infection, for sterilizing the bowel with antibiotics or restoring the normal anatomy by surgery will often improve absorption and cure the anaemia (Halsted, Lewis, and Gasster, 1956; Mollin, Booth, and Baker, 1957).

The cause of the steatorrhoea in patients with the blind-loop syndrome, or diverticulosis of the jejunum, is more difficult to explain. None the less, it must be related to the presence of bacteria, because it, too, can be improved by antibiotics or by removing the offending loop or the segment of bowel bearing the diverticula (Watkinson, Feather, Marson, and Dossett, 1959).

In patients who have suffered massive resection of the gut, the removal of up to two-thirds of the small intestine is followed by little incapacity so long as the remaining bowel is normal, and survival with only 7 inches (18 cm.) of jejunum has been recorded (Jackson, Linder, and Berman, 1951). There are a number of interesting differences between these patients and those with blind loops of bowel. Initially, there is profound loss of weight with impairment of absorption of all foodstuffs except alcohol, which is absorbed from the stomach. However, in man as in animals, hypertrophy of the remaining bowel usually occurs and the defect in absorption lessens with time. Megaloblastic anaemia is very uncommon, but in cases where the ileum has been totally removed Mollin, Booth, and Baker (1957) have shown that there is gross failure to absorb vitamin B_{12}; so presumably there must be a danger that subacute combined degeneration of the cord will develop, even if anaemia is prevented by adequate supplies of folic acid. Similarly, iron deficiency is rare unless there is bleeding, because the iron can be absorbed from the intact duodenum.

Usually hypocalcaemia and tetany are not a marked feature of massive resections. In this context (Morse, Dickson, Nonamaker, and Embree, 1959) have reported an interesting case in which the surgeon resected all but the proximal 3 feet (90 cm.) of jejunum and made small blind pouches of jejunum and colon at the time of the anastomosis. Tetany developed, and oral and intramuscular injections of calcium and large doses of vitamin D had little effect on the serum calcium. Reconstitution of the anastomosis seven months later to eliminate the blind loops of gut produced a striking improvement in the blood calcium and abolished the tetany, although the steatorrhoea continued.

In patients that survive for any length of time after massive resection, the picture is complicated by a gradual failure of pancreatic function which in turn contributes to the steatorrhoea. The cause of the atrophy of the pancreas is not known, but it may be the result of chronic malnutrition, especially of protein as occurs in kwashiorkor, or it may be due to lack of stimulation of the pancreas by secretin (Jackson, Linder, and Berman, 1951; Dreiling, 1957; Leitner, 1958).

Group 4.—Infiltration of Intestinal Mucosa (Blockage of Lymphatics)

Crohn's Disease. Tabes Mesenterica. The Lymphomata. Amyloid Disease. Systemic Sclerosis (Scleroderma). Whipple's Disease

Traditionally the steatorrhoea in this group has been attributed to blockage of lymphatics, but involvement of the mucosa is probably more important because, even in Hodgkin's disease and other lymphomatous conditions of the mesentery, not only fat but also sugar is poorly absorbed (French, 1955). In Crohn's disease and other chronic granulomata the ill effects of the underlying disease are often increased by those of resection of the gut and the formation of blind loops of bowel. In such patients the margin of safety is much less than in normal individuals, and symptoms may worsen after the removal of quite a short length of intestine. Tabes mesenterica is a much less common cause of steatorrhoea than it used to be; there were only four cases in my series. However, from time to time massive mesenteric calcification will suggest the diagnosis.

Diarrhoea and steatorrhoea have long been recognized as part of the syndrome of secondary amyloidosis, but the gut may also be involved in primary systemic amyloidosis, although such cases are rare (Bassett, Adams, Goldman, and Fishkin, 1952; Mamou, Savoie, and Damblon, 1955).

Another rare condition which may involve the intestine and lead to the development of steatorrhoea is diffuse systemic sclerosis (scleroderma). The involvement of the bowel is usually a late manifestation and is less common than changes in the skin or oesophagus. Heartburn and abdominal pain are prone to occur and diarrhoea may alternate with constipation. *X*-ray examination of the bowel shows distended coils of gut and diminished peristalsis (Rosenthal, 1957; Sommerville, Bargen, and Pugh, 1959).

It is over 50 years since Whipple first described the disease which bears his name. He reported the case of a young physician who in life had suffered from cough, loss of weight, arthralgia, and diarrhoea. At necropsy the macrophages of the lymph nodes of the mesentery and of the intestinal wall were distended with material which at first was thought to be fat (Whipple, 1907). There are now over 60 well-documented cases in the literature, and the major landmarks in our understanding of the disease have been the demonstration by Black-Schaffer (1949) that the material in the macrophages is a glycoprotein, and the discovery that the peripheral nodes and many other tissues are involved in the process (Puite and Tesluk, 1955).

We have had the opportunity to observe one of these cases closely.

The patient was admitted to hospital in 1956 at the age of 48, with a history of diarrhoea, loss of weight, and anaemia of two years' duration. Investigation revealed a profound iron deficiency and steatorrhoea; but a raised E.S.R., the presence of occult blood in the stools, and the fact that radio-iron was absorbed normally, all pointed to the steatorrhoea being secondary to an anatomical lesion of the bowel. Mr. Corry kindly carried out a laparotomy, and the typical changes of Whipple's disease were found. Fig. 2 shows the appearance of the mucosa of the jejunum with club-shaped villi containing numerous macrophages with large foamy cytoplasm distended with P.A.S.-positive material. Over the next three years his illness pursued a stormy course. Steroids failed to bring about improvement, and, although *x* rays to the abdomen seemed to produce benefit for a time, he gradually went downhill. There were episodes of severe hypokalaemia and subacute intestinal obstruction, and, finally, in his last year he developed a total gaze paralysis and episodic mental confusion. He died in November, 1959, five years after the onset of his illness. At necropsy P.A.S.-staining material was found in many tissues. Particularly interesting were the vegetations on the heart valves, which in section showed the P.A.S.-positive material, and the demonstration of the involvement of the brain and cord. Fig. 3 is a section of the thalamus

showing the presence of P.A.S.-positive material. Some of it is extracellular, but most is in close association with clumps of microglia. Fig. 4 shows the accumulation of the material in the grey matter of a pontine nucleus, also in association with microglial cells. The white matter is relatively normal.

The cause of Whipple's disease is still unknown, but three main theories have been advanced to explain it. The first, now no longer held, was that there was a basic defect in fat metabolism. The second was that an abnormal mucoprotein was produced within the lumen of the intestine and that this was absorbed and gave rise to the symptoms. This was difficult to sustain because of the fact that the arthralgias and other systemic symptoms often preceded the involvement of the gut by many years, and also because the level of seromucoids was often just as high in idiopathic steatorrhoea as in Whipple's disease. The third theory of aetiology is that

Fig. 2.—Section of jejunal mucosa (P.A.S. stain) from patient with Whipple's disease, showing club-shaped villi filled with macrophages containing P.A.S.-positive material.

Whipple's disease should be classed as a collagen disease. In support of this, Taft, Liddelow, and Ralston (1959) have put forward evidence that the abnormal material present in the macrophages may not be phagocytosed but perhaps is formed *in situ*. They showed with appropriate staining that some of the cells of the reticulo-endothelial system seemed to be producing ribonucleic acids normally, while others were producing glycoprotein, and in some there was a transition from one to the other. They could not explain why the change had occurred, but thought that it might be due to a genetic defect, as has been suggested by Puite and Tesluk (1955), or to a low-grade neoplastic process.

The idea that the disease is due to a change in the nature of the ground substance of the cells is attractive, and the pattern of distribution of the P.A.S.-positive material in the brain of my patient is more in keeping with this than with the suggestion that some abnormal substance had been filtered off from the blood-stream.

Group 5.—Infection of Bowel by Pathogens

Giardia lamblia. Candida. Coccidioides. Proteus vulgaris

This is an unimportant group numerically. The flagellate *Giardia lamblia* will produce a steatorrhoea, and the ease with which it can be eradicated by treatment with mepacrine makes it worth while to look for the cysts in the stools or for the flagellates in the duodenal aspirate (Cortner, 1959).

The part played by infection with other known pathogens is less certain. They may be important in the few cases where the steatorrhoea accompanies agammaglobulinaemia, or when the normal flora of the gut has been destroyed by a broad-spectrum antibiotic (Merliss and Hoffman, 1951).

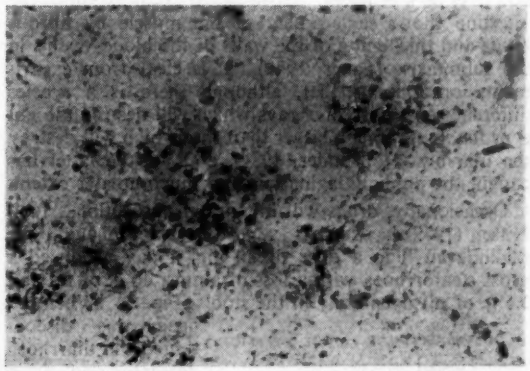

Fig. 3.—Section of thalamus from patient with Whipple's disease (P.A.S. stain), showing most of the P.A.S.-positive material is in close association with clumps of microglia.

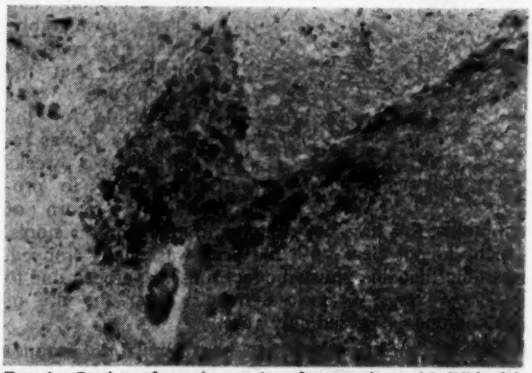

Fig. 4.—Section of pontine nucleus from patient with Whipple's disease (P.A.S. stain), showing accumulation of P.A.S.-positive material in the grey matter. The white matter is relatively normal.

Group 6.—Failure of Blood Supply

Coeliac and Mesenteric Thrombosis or Embolism

Experiments in animals have shown that failure of absorption may occur in states of shock, but it is only in the past two years that mesenteric arterial disease has been recognized as a cause of steatorrhoea in man. In 1958 Joske, Shamma'a, and Drummey reported two interesting cases in which the block in the artery was removed surgically, in one 34 hours and in the other 12 hours after the obstruction had occurred. In both, although the blood supply was restored, failure to absorb fat and other substances developed and the defect took months to recover although the acute symptoms of ischaemia rapidly subsided.

Patients with mesenteric arterial disease are prone to suffer from crampy postprandial abdominal pain, and it is likely, as occurred in one of the two in my series, that they will be diagnosed as suffering from chronic pancreatitis unless the alternative diagnosis is considered.

Group 7.—Iatrogenic Steatorrhoea

X-radiation, Drugs (Phenindione, Neomycin)

In view of the intense metabolic activity of the intestine, it is perhaps not surprising that *x*-radiation to the abdomen will impair absorption. Reeves, Sanders, Isley, Sharpe, and Baylin (1959) found that steatorrhoea developed in 13 out of 29 patients with tumours of the cervix who were given prophylactic radiation to the abdomen. In chronic cases subacute intestinal obstruction may be a problem. Histological examination of the intestine shows replacement of the muscle by fibrous tissue and thickening of the walls of the blood-vessels in the submucosa (Sauer, 1959). It is clear from experiments on animals that, although there is a species difference, the dose of *x* rays which will destroy the gut is probably not much larger than that which will destroy the marrow (Hollaender, 1954), and yet the latter has caught the public imagination to a much greater extent.

Occasionally, drugs will impair fat absorption. Juel-Jensen (1959) has reported a case in which phenindione ("dindevan") in a dose of 50 mg. a day produced a gross steatorrhoea with a loss of almost 40 g. of fat and 3.5 g. of nitrogen daily in the stools (Fig. 5). When the drug was discontinued the diarrhoea decreased and within a week the stools were normal and the fat excretion had fallen considerably. Because we were not convinced that the phenindione was responsible for the diarrhoea it was restarted two weeks later, only to produce a return of symptoms, this time with blood and mucus in the stools, which did not clear until the drug was finally stopped. I assume that this unusual effect must have been due to an idiosyncrasy, because diarrhoea after the use of phenindione is exceedingly rare.

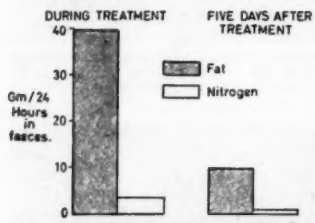

FIG. 5.—Steatorrhoea due to phenindione, showing daily excretion of fat and nitrogen in the faeces while the patient was receiving 50 mg. of phenindione daily and the fall in excretion five days after the drug was stopped.

The other drug which has been shown to produce steatorrhoea is neomycin. This interesting observation by Jacobson and his colleagues may provide the reason for the paradox that while the tetracyclines will produce an improvement in the absorption of vitamin B_{12} in patients with the blind-loop syndrome, neomycin, the most powerful intestinal antiseptic of all, will not (Doscherholmen and Hagen, 1954; Halsted, Lewis, and Gasster, 1956). The way in which it produces the steatorrhoea remains completely unknown, but there is a failure in the absorption not only of fat but also of sugar, iron, and vitamin B_{12}; and histological examination of the jejunal mucosa of the treated patients has shown varying degrees of clubbing of the villi, round-cell infiltration, and oedema of the lamina propria.

Apparently the defect in intestinal function recovers quite quickly once the antibiotic is stopped (Jacobson, Chodos, and Faloon, 1959; Jacobson, Chodos, Prior, and Faloon, 1959).

Group 8.—Miscellaneous Causes of Steatorrhoea

Diabetes Mellitus. Malignant Carcinoid Tumours. Schönlein-Henoch Purpura. Infectious Mononucleosis. Pneumatosis Cystoides

Steatorrhoea may occur in the course of diabetes mellitus. In some of the cases both are due to pancreatic failure, but in others the external secretion of the pancreas has been shown to be normal. The association of the steatorrhoea with diabetic neuropathy has led to the suggestion that the failure of absorption may be due to involvement of the autonomic nerve supply of the bowel (Berge, Wollaeger, Scholz, Rooke, and Sprague, 1956).

Steatorrhoea may occur in association with malignant carcinoid tumours of the intestine (Kowlessar, Law, and Sleisenger, 1959). The cause of the malabsorption is uncertain, but the large amount of 5-hydroxytryptamine circulating in the blood increases gastro-intestinal movements and leads to an outpouring of mucus which could well interfere with absorption (Haverback, 1958). The observation that steatorrhoea may occur in patients with carcinoid tumours may help to shed some light on one of the causes of diarrhoea in idiopathic steatorrhoea itself. In idiopathic steatorrhoea increased quantities of 5-hydroxyindole acetic acid and indole-3-acetic acid are found in the urine, presumably as a result of a breakdown in the metabolism of tryptophan (Kowlessar, Williams, Law, and Sleisenger, 1958; Haverback, Dyce, and Thomas, 1960).

There are two main ways in which this might occur. Firstly, the delay in absorption of the amino-acid tryptophan might lead to the formation of excessive quantities of tryptamine and other metabolites, or, secondly, they might be formed as a result of excessive bacterial action within the lumen of the intestine. I believe that the first explanation is the more likely, for treatment with the gluten-free diet will decrease the excretion of 5-hydroxyindole acetic acid, presumably by favouring the normal processes of absorption (Sleisenger, Law, Kowlessar, Pert, and Almy, 1958). The observation that treatment with neomycin will decrease the urinary excretion of indole-3-acetic acid (Haverback, Dyce, and Thomas, 1960) is in keeping with this rather than with the theory of abnormal bacterial activity. In the light of the findings of Jacobson and his colleagues the antibiotic could be expected to reduce absorption still further (Jacobson, Chodos, Prior, and Faloon, 1959).

The remainder in this group—infectious mononucleosis (Abrahamsen, 1954), Schönlein – Henoch purpura (Eilersen, 1959), and pneumatosis cystoides intestinalis (Yunich and Fradkin, 1958)—are very rarely associated with steatorrhoea, and I have included them only because I wish my clinical picture of the malabsorption syndromes to be complete.

Diagnosis

Now to the problem of diagnosis. The wide spectrum of possible clinical signs at first sight might well seem to make the task a hopeless one. In fact, most patients with malabsorption do pass large, pale, foul stools, and in these the diagnosis is easy. Even if the stools are normal it is decidedly unusual for the patient to complain of a single symptom, and usually the association of several, which could be due to a deficiency state, will suggest the diagnosis. Such is the variation in these cases that at one end of the scale we have patients with a resistant anaemia, or an obscure dermatitis, in whom the diagnosis is considered almost as a policy of despair, and, at the other, patients with the classical stools in whom the estimation of fat-excretion does no more than give numerical respectability to a firm clinical impression. In a syndrome as varied as this can be, the importance of a full and accurate history is paramount,

for the clues may lie as far back as a prolonged illness in infancy or a distant abdominal operation for an appendix abscess.

The results of Annegers, Boutwell, and Ivy (1948) have shown that 95% of normal persons on diets containing up to 150 g. of fat daily excrete less than 7 g. of fat per day in the stools. It is therefore possible to make the diagnosis of steatorrhoea by measurement of the excretion of fat alone without the need for elaborate balance techniques.

There is little doubt that the estimation of the output of fat in the stools is still the most certain way of making the diagnosis, but there is a real need for quick screening tests that can be applied to large groups of subjects. One of these which has given promise is measurement of the absorption of triolein and oleic acid labelled with radioactive iodine. In spite of early doubts about the suitability of radiotriolein as a test, it has been shown that the bond linking the iodine to the fat is unaffected by gastric or pancreatic juice, that there is a good correlation between the absorption curves obtained and those of vitamin A, and that it is handled, in animals at least, in the same way as tripalmitin labelled with ^{14}C.

In idiopathic steatorrhoea the absorption of both radiotriolein and radio-oleic acid is impaired. In pancreatic steatorrhoea, where the fault is primarily in the digestion of fat, triolein is poorly absorbed but oleic acid absorption is normal. In other forms of steatorrhoea the results are inconsistent (Kaplan, Edidin, Fruin, and Baker, 1958; Berkowitz, Sklaroff, Woldow, Jacobs, and Likoff, 1959; Playoust, Wyatt, and Blackburn, 1959).

In the malabsorption syndromes the impairment of fat absorption usually parallels that of other substances, but even in idiopathic steatorrhoea this is not always the case. For this reason it is important to test the absorption of more than one substance in suspected cases. Traditionally, in spite of their disadvantages, a group of oral tolerance tests have been employed for this purpose. The earliest to be used was the glucose-tolerance test, but this has fallen into disfavour with the demonstration that a high proportion of normal persons show flat curves. Butter-fat, vitamin A, and carotene have all been used, but probably the best is the D-xylose absorption test (Hunter and Prevatt, 1958).

Although xylose is not the inert substance it was formerly thought to be, in the absence of renal damage the amount appearing in the urine after an oral dose provides a good index of absorption (Christiansen, Kirsner, and Ablaza, 1959). In normal persons (Fig. 6), after an oral dose of 25 g., from 3.2 to 8.9 g., with a mean of 5.8 g., is excreted in the urine within the first five hours. In untreated idiopathic steatorrhoea the amount excreted is very much less, ranging from 1.2 to 2.1 g., with a mean of 1.7 g. In treated idiopathic steatorrhoea the excretion approaches normal, while in steatorrhoea due to gastric operations and pancreatic disease the mean excretion is exactly the same as in the normal subjects (Perry, unpublished observations). These figures are comparable to those reported by Butterworth, Perez-Santiago, Martinez-de-Jesus, and Santini (1959), who have confirmed that faulty absorption is the cause of the difference between the results obtained in untreated patients with idiopathic steatorrhoea and normal subjects; for, if the xylose is given intravenously, the urinary excretion in the next 24 hours is the same in the two groups.

In difficult cases further information may be obtained by the use of the folic-acid-excretion test (Girdwood, 1953) or from studies of the absorption of radioactive vitamin B_{12} or iron (Badenoch and Callender, 1954a; Callender and Evans, 1955).

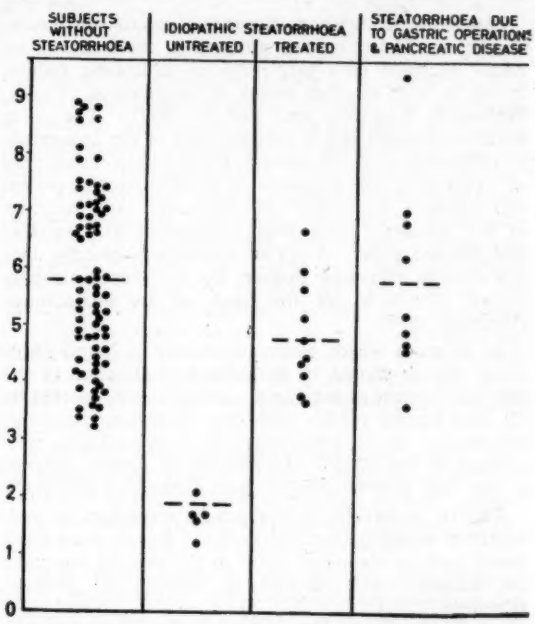

Fig. 6.—Grammes of D-xylose excreted in the urine in the first five hours after an oral dose of 25 g. in 75 control subjects without steatorrhoea, in five untreated and 10 treated patients with idiopathic steatorrhoea, and in nine patients with steatorrhoea due to pancreatic disease or gastric operations. The interrupted horizontal lines indicate the mean in each group (data of S. Perry).

The problem of the differential diagnosis of steatorrhoea has been complicated in the past by the fact that patients with idiopathic steatorrhoea have had to be diagnosed by exclusion. Unless a special search was made for pancreatic failure, occult blood was found in the stools, or one of the screening tests gave an unexpectedly normal result, as in our patient with Whipple's disease, mistakes could easily be made. For this reason careful radiological examination of the bowel should be made in every patient. There is evidence that the radiological changes which are found in idiopathic steatorrhoea depend on the presence of an excess of mucus within the lumen of the gut, and may be either clumping of barium, as is shown in Fig. 7, or a transformation of the normal feathery appearance into a ladder pattern resembling a stack of coins (Fig. 8). The type of pattern found depends, at least in part, on the barium suspension used, the ladder pattern being more common if a non-flocculable barium is employed (Ardran, French, and Mucklow, 1950). The changes are not confined to the idiopathic group, and it is not possible to make the differential diagnosis between idiopathic steatorrhoea and pancreatic steatorrhoea with safety on the *x*-ray pattern of the bowel alone. *X*-ray studies may also show an unsuspected stricture or reveal the presence of regional ileitis or systemic sclerosis.

Some of the structural lesions which can lead to steatorrhoea are extremely difficult to demonstrate. Blind loops can be overlooked and fistulae are often difficult to find, and the clumps of barium within the diverticula of the jejunum may be mistaken for floccules of medium within the lumen of the gut.

Pancreatic steatorrhoea presents a special problem in diagnosis. The output of nitrogen in the faeces is no longer accepted as a safe index of pancreatic failure. It can be high in other forms of steatorrhoea (Taylor, Wollaeger, Comfort, and Power, 1952). The most reliable screening test is measurement of the absorption of radio-oleic acid and triolein, but the only certain way of confirming the diagnosis is to intubate the patient and measure the output of bicarbonate and enzymes in the duodenal juice after stimulation with secretin and pancreozymin. A normal response to secretin does not exclude pancreatic disease, but it makes it virtually certain that it is not the cause of the steatorrhoea (Dreiling, 1957).

In all cases where pancreatic failure is found fibrocystic disease should be excluded by estimation of the chloride content of the sweat. In 140 cases reported by Di Sant'Agnese (1956), with one exception, the range of chloride in the sweat was 50 to 160 mEq/l., with a mean of 106 mEq/l. In contrast, in normal controls it was only 4 to 60 mEq/l., with a mean of 27 mEq/l.

Finally, pancreatic failure can be secondary to malnutrition resulting from steatorrhoea due to some other cause, and an abnormal result to the secretin test must be accepted with reserve in severely ill patients (Dreiling, 1957).

Biopsy of the Mucosa of the Intestine

Here the difficult matter of differential diagnosis rested until biopsy of the mucosa of the small intestine became a practical possibility. It is true that many of the earlier authors, notably Manson-Bahr (1924), thought that there were histological changes in the small intestine at least in tropical sprue, and that in 1954 Paulley published some beautiful pictures of the mucosa of the intestine in idiopathic steatorrhoea which had been obtained at laparotomy. They showed blunting of the villi, atrophy of the mucosa, and infiltration with plasma cells, but the difficulty of obtaining useful material prevented general acceptance of his views. However, the position was radically altered when Shiner (1956) introduced her peroral biopsy tube. For the first time histological examination of the mucosa was possible with little inconvenience to the patient.

Her observations fully confirmed those of Paulley. In contrast to the beautiful finger-like projections of the villi of the normal jejunum (Fig. 9), the mucosa of the small intestine in idiopathic steatorrhoea and coeliac disease is flattened and there is a reduction in absorptive surface (Fig. 10). The villi are short and blunted, there is a variable increase in the cells of their stroma, and the surface epithelium is reduced to a low columnar type with small irregular nuclei (Shiner, 1957; Sakula and Shiner, 1957). Mitoses are more common than usual, and Shiner and Doniach (1959) have suggested that in the coeliac syndrome the cells of the mucosa of the intestine may have a shorter life-span than in normal persons and that desquamation takes place at a faster rate.

In other forms of steatorrhoea when the malabsorption is secondary to pancreatic failure, follows gastric resection, or is symptomatic of a wider pathological process, the mucosa of the jejunum is usually normal and villous atrophy is variable and inconsistent (Shiner, 1957; Baird and Dodge, 1957; Paulley, Fairweather, and Leeming, 1957; Joske and Blackwell, 1959).

Rubin and his colleagues, in two careful studies, have taken the matter further (Rubin, Brandborg, Phelps, and Taylor, 1960; Rubin, Brandborg, Phelps, Taylor, Stemler, Murray, Howry, and Volwiler, 1960). They

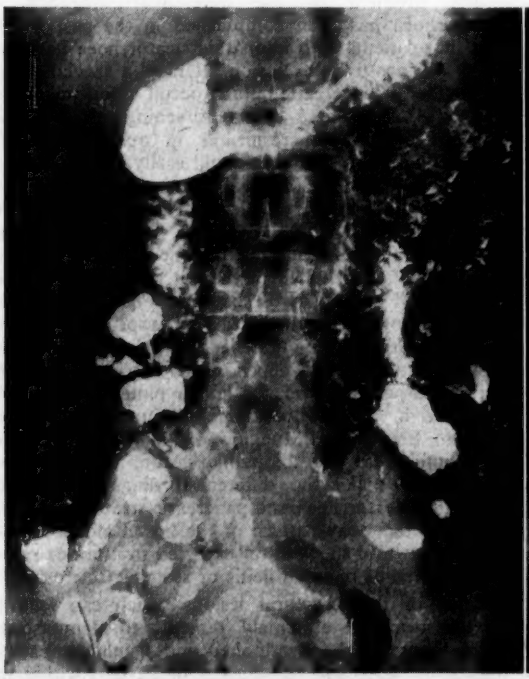

Fig. 7

Fig. 8

Figs. 7 and 8.—Small-bowel patterns in the presence of steatorrhoea showing either clumping of barium (Fig. 7, left) or transformation of the normal feathery appearance into a ladder pattern (Fig. 8, right).

agree that the lesion in idiopathic steatorrhoea and coeliac disease, and probably also in tropical sprue, is the same, although in the latter there may be a heavier infiltration with inflammatory cells. They maintain that the best criterion on which to base the diagnosis is a decrease in the overall length of the absorptive surface of the jejunum. By taking up to 10 biopsies from different areas of bowel in the same individual they showed that the degree of change could vary from one part of the duodenum and jejunum to another, but that the lesion was clearly diffuse and involved the whole of the upper small intestine. To their surprise, in two patients in whom the jejunum showed the lesion, biopsies of the ileum were normal. They stress the importance of taking multiple biopsies, because blunted flattened villi were sometimes found in normal persons over Brunner's glands or over lymphoid follicles, and occasionally a very similar picture was found in Crohn's disease, although here the changes were patchy and not diffuse.

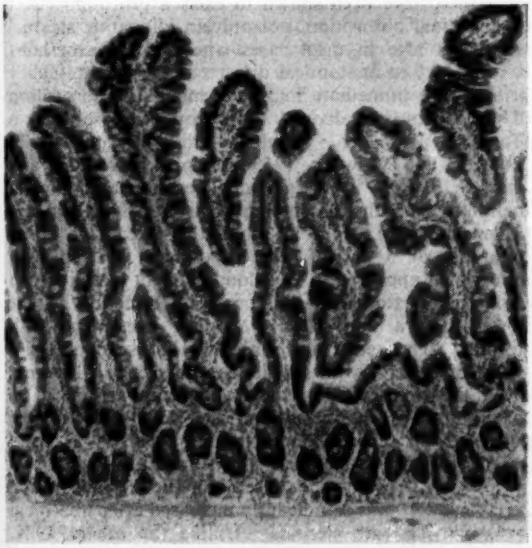

FIG. 9.—Section of normal jejunum stained with H. and E., showing finger-like villi lined with tall columnar epithelium.

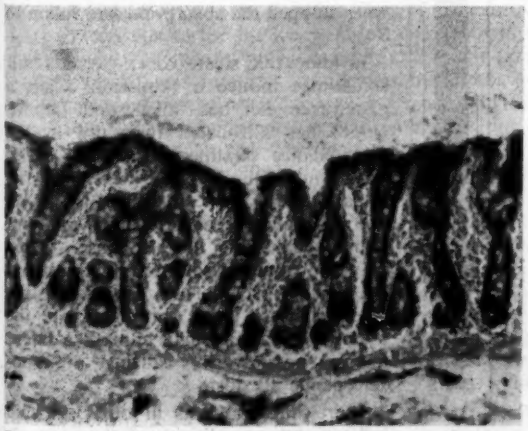

FIG. 10.—Section of jejunum from idiopathic steatorrhoea stained with H. and E., showing blunting of villi, reduction of absorptive surface, and cellular infiltration of stroma.

The effect of treatment with the gluten-free diet or steroids on the histological picture of the small intestine in the coeliac syndrome is still uncertain, but the weight of evidence suggests that in the majority of patients the lesion persists throughout life and is uninfluenced by treatment. Kelley and Terry (1958) found no improvement in one case after 14 months' treatment with steroids and a gluten-free diet, and neither Rubin and his colleagues nor Shiner and Doniach could detect any differences between the treated and untreated cases. Rubin did, however, biopsy the jejunum in six children who were clinically normal but were said to have had coeliac disease in the past, and found the mucosa normal in every case. It may be, therefore, that if the patients are put on a gluten-free diet early enough in the course of the disease, histological recovery can take place.

In tropical sprue the available evidence suggests that the state of the mucosa improves with treatment. It is not yet known whether it becomes entirely normal when the patient is cured (Shiner and Doniach, 1959; Butterworth, Smith, and Perez-Santiago, 1959).

Peroral biopsy of the intestine has been a big advance, but in patients with progressive disease in whom the histology of the gut is normal, laparotomy may still be needed to establish the diagnosis. That this is more than an academic exercise is underlined by the few patients in whom the discovery of an unsuspected fistula, or an adenoma of the pancreas, has led to effective treatment when other measures have failed.

Treatment

The management of idiopathic steatorrhoea has been revolutionized by the introduction of the gluten-free diet. In view of the country of origin of Gee's miraculous mussels so many years ago, it is fitting that it is to a Dutch paediatrician that we owe this major advance in treatment (Dicke, 1950). The effectiveness of the diet is now well established, not only in the cases in childhood, but also in the great majority of those who develop the disease in adult life, although in the adults the time taken to recover may be measured in months rather than days or weeks (French, Hawkins, and Smith, 1957). In the patients that respond the effect is dramatic. Fat-absorption improves, the nitrogen and calcium balances become positive, and the high faecal losses of sodium, potassium, phosphorus, and magnesium are reduced (Schwartz, Sleisenger, Pert, Roberts, Randall, and Almy, 1957). There is improvement in the absorption of vitamin B_{12} (Mollin, Booth, and Baker, 1957) and iron (Badenoch and Callender, 1960), and the levels of plasma proteins rise and oedema disappears (Forshaw, 1957). The absorption of xylose is also increased (Finlay and Wightman, 1958), and I suspect that the flat glucose-tolerance curves which sometimes persist in patients on the gluten-free diet are an indication not of impaired absorption but of the increased tolerance to sugar which was present before treatment was begun.

When I look at the flattened, shrunken epithelial surface of the intestine in the gluten enteropathy, I am lost in wonder at the functional reserve which allows substances of every kind to pour across the mucous membrane once the offending agent is removed from its surface. Presumably the site of action is the mucosal surface, and yet some contend that the sensitivity to wheat gluten may involve a disturbance of intermediary metabolism as well.

Paediatricians have remarked that the temperament of children on the gluten-free diet changes too quickly to be the result of improved absorption, and others have noted the great speed of the haematological response. Personally, I still have to be convinced. Many must have watched the change that can occur in a patient with pernicious anaemia after parenteral vitamin B_{12} long before the blood improves, and it may well be that, in the coeliac syndrome, immediately the barrier is down the body can replenish stores of vitamins long since depleted.

The gluten-free diet has proved so successful that it has supplanted all other forms of treatment in suitable cases. On the other hand, its very success has brought new dangers. Fletcher and McCririck (1958) have pointed out that wheat flour provides almost one-third of the protein, calcium, and iron in our national diet, and, in growing children at least, supplements of these, and of the B vitamins also, will be necessary if wheat flour is withdrawn.

The restriction of wheat gluten has to be virtually absolute if the diet is to be effective, and the second danger is that the patient will take the diet intermittently, and, lacking the vitamin and mineral supplements provided by the traditional regime, will suffer a relapse. This happened to one of our patients who had a severe haemorrhage from vitamin-K deficiency. In the majority the diet will induce a full clinical remission, but the power to absorb fat and other substances may not always be fully restored, and further experience may indicate that vitamin supplements are still required (Green, Wollaeger, Scudamore, and Power, 1959). Moreover, no one will deny that it is a troublesome regime for those who have to eat away from home. For those patients as well as for all with structural disease of the bowel, the traditional high-protein and low-fat diet with vitamin and mineral supplements still has its place. Multiple vitamin deficiencies are so common that this syndrome provides one of the few rational indications for shotgun therapy (see Table). Whole B complex, vitamins C, A, D, and K, the last in water-soluble form, and vitamin E, are all required. Calcium to be effective must be given in very large doses —15 to 20 g. a day. As the anaemia is usually the result of a combined deficiency of folic acid, vitamin B_{12}, and iron, all three haematinics should be given. In severe cases, when the function of the bowel is grossly disorganized, it may be necessary to give all the substances parenterally if a rapid remission is to be obtained.

Medical Regime for Treatment of Steatorrhoea

High-calorie, high-protein, low-fat diet (supplemented with high-protein milk powder)

Tab. aneurin. co. fort.	1	t.d.s. by mouth
Folic acid	20	mg. daily by mouth
Ascorbic acid	50	,, ,, ,,
Vitamin A	4,000	I.U. ,, ,,
,, D	10,000	,, ,, ,,
,, K (water-soluble)	20	mg. ,, ,,
,, E	100	,, ,, ,,
Calcium gluconate	15	g. ,, ,,
Ferrous gluconate	1·0	,, ,, ,,
Potassium chloride	2·0	,, ,, ,,
Vitamin B_{12}	100	µg. monthly intramuscularly

Since they were first introduced nine years ago, A.C.T.H. and cortisone, and more recently its newer analogues, have been shown to exert a profound effect on intestinal absorption, not only in idiopathic steatorrhoea but also in most cases where the steatorrhoea is secondary to anatomical disease of the bowel. They bring about immediate improvement in the absorption of fat, nitrogen, calcium, and many other substances (Taylor, Wollaeger, Comfort, and Power, 1952; MacKay and Volwiler, 1955; Drenick, Hvolboll, and Halsted, 1955). Dr. Callender and I have studied their effect on the absorption of iron (Badenoch and Callender, 1960). Fig. 11 shows the percentage of an oral dose of 5 mg. of ferrous sulphate labelled with ^{59}Fe which appeared in the blood of eight patients with idiopathic steatorrhoea and one with resection of the bowel, before and after five days' treatment with steroids. The mean and observed limits found in a group of patients with simple iron deficiency who were given the iron alone is shown for comparison. The maximum absorption without steroids, even in the patients with severe iron deficiency, was 8% as compared with an average of 60% in simple iron deficiency. With one exception (B.W.), absorption was significantly increased after treatment with steroids. Unlike the others, G.K. had been on the steroids for a year, and during treatment she absorbed 37% of the dose. One week after the steroids were stopped the absorption had fallen to 8%.

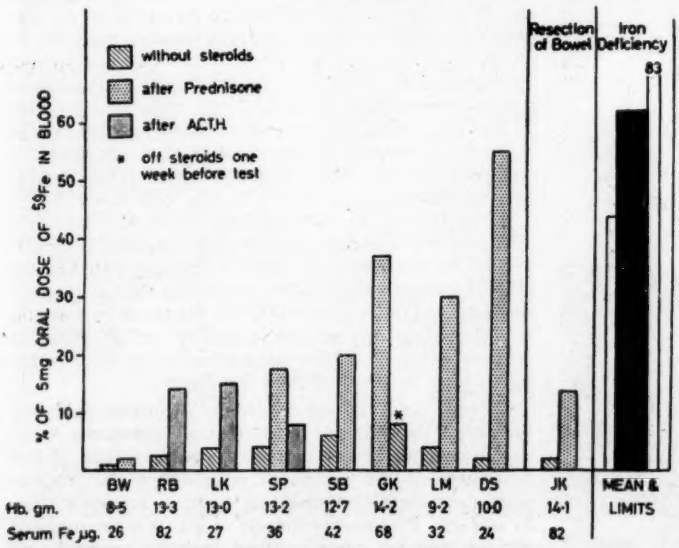
without steroids
after Prednisone
after A.C.T.H.
* off steroids one week before test
% OF 5mg ORAL DOSE OF 59Fe IN BLOOD
10
20
30
40
50
60
Resection of Bowel
Iron Deficiency
83
BW RB LK SP SB GK LM DS JK MEAN & LIMITS
Hb. gm. 8·5 13·3 13·0 13·2 12·7 14·2 9·2 10·0 14·1
Serum Fe µg. 26 82 27 36 42 68 32 24 82

FIG. 11.—Effect of administration of prednisone and A.C.T.H. on absorption from oral dose of 5 mg. ^{59}Fe in eight patients with idiopathic steatorrhoea and one with resection of bowel. Mean and observed limits found in a group of patients with simple iron deficiency not receiving steroids is shown for comparison.

In idiopathic steatorrhoea steroids will sometimes induce a remission when a gluten-free diet has failed, and Lepore (1958) has advocated their use in the maintenance treatment of severe cases. This is not without risk. Water retention is particularly prone to follow their use, and I have seen fits and transient papilloedema due to this cause. They may contribute to softening of the bones by adding osteoporosis to an existing osteomalacia. They can aggravate the hypokalaemia, and may unmask a latent tetany, possibly by causing a hypochloraemic alkalosis.

More important, as in other chronic inflammatory conditions of the stomach and intestine, perforation and peritonitis may occur with minimal warning, and

there is a report in the literature of one fatal case in which there seemed to be a link between protracted treatment with steroids and the extensive ulceration of the bowel which caused death (Himes, Gabriel, and Adlersberg, 1957).

There are some types of steatorrhoea which require special treatment.

In biliary obstruction and pancreatic failure, replacement of bile salts and pancreatic ferments may help a little if diarrhoea can be avoided. These patients often thrive better on a fairly high fat intake so long as the diarrhoea is not too troublesome and fat-soluble vitamins are supplied.

The steatorrhoea occurring after gastric operations can be minimized by retaining as big a pouch of stomach as possible, by designing operations to avoid dilatation of the afferent loop, by avoiding high-carbohydrate meals, and by the use of small doses of acid to stimulate the pancreas.

In regional ileitis and other granulomata when surgery is necessary, as much of the bowel should be preserved as possible, and it is better to anastomose the cut end of the small intestine to the lower ascending colon rather than to make the traditional ileo-transverse colostomy. Above all, the creation of blind loops should be avoided unless they are a surgical necessity.

Jejunal diverticulosis often gives rise to troublesome abdominal pain, and it may be possible to bring relief by resecting the affected segment of bowel (Watkinson, Feather, Marson, and Dossett, 1959).

Finally, steroids may bring about a temporary remission in Whipple's disease. If they fail, some improvement may follow *x* rays to the abdomen or a course of nitrogen mustard (Gross, Wollaeger, Sauer, Huizenga, Dahlin, and Power, 1959).

Conclusion

In conclusion let me look back across the ground that has been covered in the past decade, for there must lie the keys to future progress.

On a humble plain, we have learnt much about the clinical picture of steatorrhoea and are now aware that dangerous symptoms may arise whenever fat-absorption is impaired.

More important perhaps, we have begun to break with the tradition that the manifestations of steatorrhoea are always due to the failure of absorption of essential substances. We are learning that they can be the result of increased loss into the gastro-intestinal tract, and new evidence has given added point to the old idea that some of the symptoms, at least, might be due to the absorption of toxins formed within the lumen of the intestine by chemical degradation or abnormal bacterial action.

As so often in the past, it is to the careful clinical observation of one man that we owe the major breakthrough in recent years.

It may seem a far cry from a group of hungry children in the German-occupied Netherlands to the careful research which is defining ever more closely the basic defect in the gluten-enteropathy, but the links in the chain are there.

Gradually a new concept is arising, and it may be that in future years we will classify the coeliac syndrome as an inborn error of metabolism differing from others that we recognize only the fact that the lesion lies not in the liver or the kidney but in the wall of the small intestine.

I am grateful to my colleagues, the physicians and surgeons of the United Oxford Hospitals, for permission to study their cases; to Miss M. C. McLarty for preparation of the diagrams; to Mr. E. L. Tugwell and Miss A. L. Habden for the clinical photographs and preparation of the slides; to Miss J. W. Dearberg for help in preparing the script; and to Dr. S. T. Callender and Professor L. J. Witts for their helpful advice and criticism.

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Research grants totalling over $523,000 have already been made to 40 scientists in 1960 by the Tobacco Industry Research Committee of the United States of America. Among the factors being studied are the possible interaction of viruses and tobacco smoke, environmental factors and pulmonary disease, coronary artery disease, psychological differences between smokers and non-smokers, characteristics of aromatic hydrocarbons, the effect of tobacco derivatives on arterial and myocardial tissue cultures, the role of the nucleolus in normal and malignant cells, and the effect of negatively charged ions on human tracheo-bronchial ciliary action. All grants are made by the Scientific Advisory Board, composed of nine doctors, scientists, and educators, who retain their institutional affiliations, under the chairmanship of Dr. K. MERRILL LYNCH, chancellor of the Medical College of South Carolina, Charleston.

THE CHEMICAL DIAGNOSIS OF STEATORRHOEA

BY

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The term "steatorrhoea" was introduced by Kuntzmann in 1824 to describe specimens of faeces in which globules of fat were visible to the naked eye. It has long been known that there may be an excess of faecal fat which is not visibly obvious, and the term is now generally used to include such specimens. Apart from those cases of gross steatorrhoea where the condition is at once obvious, the diagnosis of this condition is entirely dependent on chemical methods of analysis, and the interpretation of results is made very difficult by the problem of individual variation and by vague definitions and bad nomenclature. The main difficulties of interpretation are these:

(*a*) The bowel habits of different individuals, and of the same individual at different times, vary considerably. The excreted mass is inhomogeneous, which immediately introduces all the errors of sampling; and even in normal subjects the amount of fat excreted per day (no matter how the results are expressed) is known to vary within wide limits.

(*b*) The term steatorrhoea means, literally, an excess of fat in the faeces, but this in turn may mean one or other of two quite different things: either an abnormally high percentage of fat in the dried specimen or an abnormally high daily excretion of faecal fat. These two quantities are not the same, and, what is much more important, they can vary independently.

(*c*) The expression "fat balance" is commonly used to describe the correlation between the amount of fat excreted per day over a given period and the dietary fat intake, when this intake is fixed at a given value, generally in the region of 50–75 g. per day. A balance experiment is a well-defined scientific procedure used in the investigation of total metabolism, and the so-called "fat balance" is not a balance experiment in any sense of the term. This most unfortunate nomenclature not only is the cause of much confusion but makes it almost impossible to interpret many of the experimental results found in the literature. However, since the expression is so thoroughly established in general use, it will be retained here—under protest.

(*d*) The fat which is excreted in the faeces has little relationship, if any, to the dietary fat in normal animals. Hill and Bloor (1922) showed conclusively that the quantity of faecal fat was reasonably constant in any given animal (their experiments were carried out on cats) and was virtually independent of the amount of fat in the diet. These findings have been confirmed by many others, and particularly, in normal human subjects, by Annegers, Boutwell, and Ivy (1948), whose paper on the subject leaves no room for doubt.

(*e*) Sperry (1929) showed that a substantial part, estimated at up to 40%, of the faecal fat was derived from the bacteria in the lower intestine and was presumably the result of bacterial synthesis. It is also well known that gut-sterilizing drugs such as sulphaguanidine and terramycin bring about a considerable drop in the percentage of fat in the faeces. More recently, Sammons, Vaughan, and Frazer (1956) have isolated a strain of *Streptococcus faecalis* which can synthesize large amounts of long-chain fatty acids *in vitro*.

(*f*) And, lastly, there is evidence that the bowel mucosa can actively secrete fat into the lumen (Lewis and Partin, 1954).

Establishing a diagnosis of steatorrhoea now goes far beyond the recognition of coeliac disease in children and idiopathic steatorrhoea in adults. It is a matter of some importance in many disorders, such as the post-gastrectomy syndrome, the malabsorption syndrome, certain disturbances of calcium and of iron metabolism, and other equally ill-defined conditions, and certain lines of research into these disorders involve the investigation of a possible state of steatorrhoea.

The data presented here are the results of fat-balance experiments dealt with by this department over a period of two years. The object of this survey was to decide how far chemical analysis could assist in establishing or rejecting a diagnosis of steatorrhoea, and, at the same time, to decide between the relative merits of a fat analysis of a random specimen of faeces and the results obtained by a fat balance. No attempt has been made to correlate the clinical diagnosis with the chemical results. All cases of *gross* steatorrhoea, where the diagnosis was not in dispute, have been excluded from this survey, which is concerned only with those cases where the question of steatorrhoea had been raised by the clinician and material sent to the biochemist in an attempt to provide the answer.

Subjects and Method

All the subjects were in-patients admitted for a variety of reasons, and, with one exception, all were adults. As stated above, all cases of severe steatorrhoea where the diagnosis could be made by inspection of the faeces have been omitted from consideration, since they do not constitute any diagnostic problem which requires reference to a biochemist. The subjects included two separate series of cases which were admitted for special investigations—namely, a series of post-gastrectomy cases and a series of cases of osteoporosis. The other cases were the usual miscellaneous collection to be found in any general hospital and in which a state of steatorrhoea was at least possible.

The patients were placed on a mixed diet containing 70–75 g. of fat per day, and a few days' equilibration was allowed before collection of specimens was started. The bowel wash-out procedure was *not* used, as experience had shown that it invariably resulted in a state of complete constipation for several days. Markers were not used, but emptying of the bowel was as complete as could reasonably be expected. The usual precautions were taken to avoid the use of purgatives (especially paraffin oil), contamination with barium sulphate, carrying out experiments on any patient suffering from diarrhoea, or experiments on any patients undergoing a therapeutic course of gut-sterilizing drugs.

The length of the "balance period" varied from three to seven days. This is much less than the optimal period, and, as Annegers *et al.* (1948) have so clearly shown, the shorter the balance period, the greater the normal range of variation of results. But in a general hospital one is clearly limited both by the ward and by the laboratory facilities, and the object of the exercise is simply to confirm or reject a diagnosis of steatorrhoea.

In all, 138 patients were studied and 231 fat balances were carried out. In 66 of these patients a fat balance was carried out more than once, and this immediately raised the question of whether each fat balance should be considered separately, or whether all the fat balances done on any one patient should be combined into one

result—the latter especially in those cases where two or more fat balances had been carried out in immediate succession. There are several arguments for and against, but it was finally decided to consider each fat balance separately, since there was often a long period of time between the balances, many of the subjects had started some form of therapy between the balance periods, and, in some cases, after the initial fat balance, gluten was added to the diet to find out if it would induce a steatorrhoea. In such cases, both the clinician and the biochemist are equally interested in any change in fat excretion which may occur.

Estimation of Faecal Fat

The entire faecal mass was evaporated to dryness on the steam bath. The dried mass was then stirred up with 100 ml. ethyl alcohol containing 0.5% (v/v) concentrated hydrochloric acid in order to liberate free fatty acids from soaps, and again evaporated to dryness. When dry, the material was transferred to a large mortar and thoroughly ground up. 2 g. of the powder was weighed out, placed in a smaller mortar, and re-ground with a little silver sand which had previously been extracted with ether. This mixture was transferred quantitatively to a Soxhlet thimble and extracted with diethyl ether for four to five hours in a Soxhlet apparatus. The ether was evaporated off from the extract, and the residue was dissolved in petroleum ether (b.p. 40–60° C.). The petroleum-ether extract was filtered through paper into a tared flask, the solvent evaporated off, the flask cooled and dried in a desiccator, and weighed. The results are expressed as g. fat per 100 g. dried faeces, commonly referred to as the "percentage faecal fat." The total weight of the dried faecal mass was also determined, and, knowing the number of days over which the balance extended, the daily fat excretion was calculated.

This method determines the total ether- and petroleum-ether-soluble lipoid, and includes steroids, steroid esters, carotenoids, higher alcohols, etc. It is often stated that certain volatile (? fatty) acids are lost during the drying process. Any loss from this source is unlikely to be very great, since the main part of the drying is carried out before addition of acid, at which time the fatty acids are present in the form of non-volatile soaps. Any small error due to loss during the second evaporation is partly counterbalanced by the extreme efficiency of extraction in the Soxhlet apparatus compared with "wet" extraction. It might also be added that the b.p. of the 4-carbon compound *n*-butyric acid is 163° C.

Standards of Reference

In spite of the wide individual variation, it seems to be generally accepted that normal adult faeces usually contain 10–25 g. fat per 100 g. dried specimen (10–25% fat). This is the range quoted by Stewart and Dunlop (1958) and by King and Wootton (1956). Cantarow and Trumper (1955) give a range of 15–25% of the dry weight, while Varley (1958) quotes no lower limit but agrees with an upper limit of 25% fat in the dried specimen. Certainly, from the analyses recorded in this survey, the lower limit is frequently less than 10% of the dry weight, but, so far as the diagnosis of steatorrhoea is concerned, only the upper limit is important. For the purposes of classification of results, any specimen containing 25% of fat, or more, will be regarded as "abnormal."

The weight of fat excreted per day by the normal adult is a much more doubtful quantity. Most estimates have been quoted in terms of the "percentage fat absorption"—an expression of very questionable validity—but when expressed in this way all authors seem to be agreed that the "percentage absorption" in the normal individual should be not less than 90%, and several suggest a value of 95%, or more. It is implied (but seldom stated) that the 10%, or the 5%, of fat which is not absorbed is excreted in the faeces. On this basis, if the daily fat intake be fixed at 70 g., and the percentage fat absorption is 95%, the daily fat excretion should be 3.5 g.

There are few data of the actual amount of fat excreted per day by the normal adult. Those figures which appear to be most reliable are summarized in Table I.

Table I.—*Daily Fat Excretion by Normal Healthy Adults*

Reference	No. of Subjects	No. of Experiments	Daily Fat Intake	Total Fat Excreted (g. per Day)
Cooke *et al.* (1946)	41	50	50 g.	2·5±2·0
Wollaeger *et al.* (1947)	11	11	102 g.	4·1±0·5
Annegers *et al.* (1948)	40	220	93–168 g.	3·9 (s.d.=1·0)

The normal upper limits are taken as 4·5 g., 4·6 g., and 5·9 g. respectively (mean=5.0 g.).

For the purposes of classifying results, any specimens corresponding to an excretion of 5 g. of fat, or more, per day will be regarded as abnormal. On an intake of 70–75 g. of fat per day, such an excretion would correspond to a "percentage fat absorption" of 93%.

It is inevitable that any classification of data based on such arbitrary limits of normality must lead to a number of borderline cases; but it was found that a subdivision of analytical results, based on the standards of reference quoted above, gave remarkably few borderline cases.

The fat analysis of a single random specimen of faeces has the great advantage that the result depends solely on analytical accuracy; the disadvantage is that it gives no indication in most cases of the daily excretion of fat unless the result is either very high or very low. The daily excretion of fat can be obtained only from the analysis of the total output of faeces, which carries the disadvantage that it introduces a second variable—the completeness of the collection of the specimen, or, put in another way, this second variable is the average dry weight of faeces excreted per day. The introduction of this second variable is extremely important, and it is invariably ignored. For example, a patient may have a normal percentage of fat in the faeces, yet if the bulk of the dried specimen is greater than normal, the daily fat excretion may be above the accepted normal upper limit. Since these two quantities (the percentage of fat in the faeces and the total fat excreted per day) can vary independently, there are four possible combinations of results, and for the purposes of classification these will be referred to as groups A, B, C, and D.

Group A.—Faecal fat less than 25% of the dry weight; fat excretion less than 5 g. per day.

Group B.—Faecal fat less than 25% of the dry weight; fat excretion of 5 g. per day, or more.

Group C.—Faecal fat of 25%, or more, of the dry weight; fat excretion less than 5 g. per day.

Group D.—Faecal fat of 25%, or more, of the dry weight; fat excretion of 5 g. per day, or more.

The subjects in group A are clearly not cases of steatorrhoea on either count. The subjects in group D were suffering from steatorrhoea at the time when the experiment was carried out, no matter which of the two definitions of steatorrhoea is used. The cases in groups B and C may be either normal or abnormal.

Results

Since the upper limits of the "normal" percentage of faecal fat and of the "normal" daily fat excretion have been decided in advance, it is pointless to quote any standard deviations, etc., and only the mean values for each group need be considered. When classified according to the limits described above, the results were those set out in Table II.

TABLE II.—*Fat Excretion of Patients Suspected of Having Steatorrhoea. 138 patients. Total Number of Fat Balances, 231*

Group:	A	B	C	D
No. of Balances:	159	24	25	23
Percentage fat in the dried specimen	13·4%	19·7%	30·2%	29·6%
Daily excretion of fat ..	2·1 g.	8·2 g.	3·1 g.	7·2 g.
Dry weight of faeces excreted per day	16·9 g.	40·5 g.	10·5 g.	24·4 g.

Group A

The number of cases which could be regarded as bordering on the other three groups was surprisingly small. Of the 159 cases, 141 (89%) had a percentage fat less than 20% of the dry weight, and 147 (92%) had a total fat excretion of less than 4 g. per day. In 132 cases (83%) the percentage fat was less than 20% of the dry weight, *and* the fat excretion was less than 4 g. per day, so that any possibility of steatorrhoea could be completely ruled out. Indeed, in only four of the 159 cases did the percentage fat lie between 20 and 25% of the dry weight *and* the daily fat excretion between 4 and 5 g. in the same balance experiment, and only in these four cases could a diagnosis of steatorrhoea be seriously considered.

In this group the average dry weight of faecal material passed per day was 16.9 g., the extreme limits being 1 and 70 g. In 133 (84%) of these 159 cases the average dry weight of faecal excretion lay between 5 and 25 g. per day. The "normal" dry weight of total solids excreted per day was found by Wollaeger, Comfort, and Osterberg (1947) to be 27.6 ± 2.2 g., with an observed range of 13.6 to 39.1 g. (11 subjects). Diao and Johnston (1957) found a mean value of 20.9 g., with an observed range of 14.3 to 26.5 g. (9 subjects).

The cases in this group cannot be regarded as "controls," nor are they a series of normal healthy individuals, since in every case there was some clinical ground for suspecting that fat excretion might be abnormal. On the other hand, since it is quite clear that 97% of the subjects were *not* suffering from steatorrhoea, they can be used as a basis for comparison with the other three groups.

The *lower* "normal" limit for the percentage of fat in the dried faeces is generally quoted as 10 to 15%. Of the 159 analyses in this group, 42 (26%) had a percentage faecal fat less than 10% of the dry weight—and that in a group where there was at least a clinical suspicion of the possibility of steatorrhoea. It is suggested that a lower limit of even 10% of fat in the dried specimen is much too high, and should be reduced to 5% fat.

Group B

Although in this group the average percentage of fat (19.7%) in the dried faeces is much higher than the average for the cases in group A, the figure is still well within the accepted limits of normality. But of these 24 cases, only 11 had a faecal fat less than 20% of the dry weight (compared with 141 out of 159 such cases in group A). More than half the cases in this group had a "high normal" percentage of faecal fat—that is, between 20 and 25% fat.

The average daily fat excretion (8.2 g.) was as high as 15.3 g. in one case, and in almost half the cases (11 out of 24) the daily fat excretion was greater than 7 g.

The abnormally high daily fat excretion in this group is directly due to the large faecal mass. The average weight of dry faecal material excreted per day was 40.5 g., which is more than double the corresponding figure for the subjects in group A. In group B the observed range was 21 to 68 g. There is good evidence for the conclusion that these cases are, in fact, cases of steatorrhoea (see below).

Group C

The average percentage of faecal fat (30.2%) in this group is well above the accepted upper limit of normality; but if this were the sole criterion used, many of the cases in group C would have to be regarded as borderline. In 8 of the 25 cases the percentage faecal fat lay between 25 and 27% of the dry weight.

The average daily fat excretion (3.1 g.) was little greater than the corresponding value for the cases of group A, and in 18 of the 25 cases the excretion of fat was less than 4 g. per day. The finding of a normal daily fat excretion in group C is directly due to the small daily faecal mass. The average weight of dry faecal material passed per day was only 10.5 g. In spite of the abnormally high percentage fat, there are good reasons for believing that the cases in this group are not suffering from steatorrhoea (see below).

Group D

This group has been confined to cases in which a diagnosis of steatorrhoea had to be made on analytical grounds. As stated above, all cases of gross steatorrhoea were excluded from this series, so that the mean values recorded in Table II do not appear to be very striking. It will be noticed that the average percentage faecal fat is not very different from the corresponding figure for the cases in group C, and that the daily fat excretion is not very different from the corresponding figure for the cases in group B.

Repeated Fat Balances

In 66 of the patients the fat balance was repeated at least once. In 45 (67%) of these cases agreement was satisfactory and there was no doubt about the group into which the result should be placed. In 10 cases agreement was very close, and Case 59 (Table III) shows an example of a typical borderline case where two different balances fell into separate groups. In 7 cases agreement was poor, but the change in fat excretion could be ascribed to therapy—for example, the decreasing steatorrhoea in Case 103. In the remaining 4 cases the lack of agreement was due to a considerable change in the bulk of the faecal material excreted—for example, Case 128.

The last case quoted in Table III (Case 29) will be referred to later in the text.

Table III.—*Examples of Repeated Fat Balances*

Case	Balance	Percentage Fat	Fat Excreted per Day	Dry Weight of Faeces per Day	Group
59	1	23·1	5·8 g.	25 g.	B
	2	26·1	5·2 ,,	20 ,,	D
103	1	28·5	12·4 ,,	44 ,,	D
	2	23·9	15·3 ,,	64 ,,	B
	3	14·9	9·1 ,,	61 ,,	B
	4	10·3	5·6 ,,	54 ,,	B
128	1	25·6	7·3 ,,	28 ,,	D
	2	29·5	2·4 ,,	8 ,,	C
29	1	1·0	0·7 ,,	70 ,,	A
	2	2·6	1·4 ,,	56 ,,	A
	3	2·5	0·9 ,,	35 ,,	A
	4	5·4	1·1 ,,	20 ,,	A

Discussion

The great preponderance of results falling into group A shows that a diagnosis of steatorrhoea is proposed much oftener than it can be substantiated. On the other hand, it is very important in many cases to exclude the possibility of steatorrhoea. If the percentage of cases falling into group A appears unduly high, it must also be remembered that in cases of gross steatorrhoea there is no virtue in chemical analyses to support a diagnosis which is clearly obvious, and, even if the clinician is following the effects of therapy, inspection of the faecal mass in these cases is generally sufficient for the purpose. It must be admitted, however, that there are occasions when the clinician persists in attempting to demonstrate a state of steatorrhoea where the condition does not exist. Case 29 (Table III) is an example. This was a case of very severe osteomalacia with many very interesting biochemical findings—but steatorrhoea was not one of them.

In this survey the most interesting cases are those of groups B and C. Either, or both, could be regarded as cases of steatorrhoea depending on the definition.

Group B

If steatorrhoea be defined as the excretion of more than 5 g. of fat per day on an average diet, then all the patients in this group must be regarded as cases of steatorrhoea. But they are placed in this category only by virtue of the large mass of faecal residue excreted per day. It could be argued that any normal individual might land in this group simply by excreting a sufficiently large quantity of faeces. If the percentage faecal fat is 13.4% (the mean of the cases in group A) a normal individual would require to pass 38 g. of faecal solids per day in order to qualify for group B and a label of steatorrhoea. But the excretion of 38 g. of faecal solids per day is more than twice the average for the cases of group A, and of the 159 cases in group A, only 6 excreted more than 38 g. of dry faecal residue per day. This cannot therefore be accepted as a logical argument, and other considerations lead to the conclusion that the subjects in group B are indeed cases of steatorrhoea.

The average daily fat excretion of the cases of group B was 8.2 g., which is four times the average for the cases of group A, and, as it so happened, this figure was also higher than the corresponding figure for the undoubted cases of steatorrhoea in group D (although if all the cases of gross steatorrhoea had been included the figures for the cases of group D would have been very different). The percentage faecal fat was within normal limits, but more than half the cases (13 out of 24) had values in the upper normal range of 20 to 25% fat. This compares very badly with 18 out of 159 corresponding cases in group A. The association between steatorrhoea and the passage of bulky faeces has long been recognized. The average weight of dry faecal material passed by the cases in group B was almost 2½ times the corresponding figure for the cases of group A, and it was also considerably higher than the value for the established cases of steatorrhoea in group D. As a general rule, the total daily amount of any substance excreted from the body is of more fundamental importance than the concentration of that particular substance in the excretion. This has been well established in studies of urinary constituents, and no doubt applies also to faeces, although one would not care to push the analogy too far. The "percentage faecal fat" is strictly analogous, however, to a concentration.

All these considerations point strongly to the conclusion that the cases of group B are cases of steatorrhoea.

Group C

The cases of group C qualify for a diagnosis of steatorrhoea only because of the abnormally high concentration of fat in the dried faeces.

In spite of the high concentration of fat in the dried specimen, the daily output of fat is low, and is nearer to the corresponding value for the cases of group A (2.1 g.) than to the agreed upper normal limit (5 g.). The average dry weight of faecal solids (10.5 g.) was much less than the figure for the cases of group A, and the most obvious explanation is that the diet was deficient in indigestible residue. But since all four groups of patients were on approximately the same hospital diet, this cannot be the reason. Another more likely possibility is that breakdown and absorption of carbohydrate and protein was more complete than normal. This possibility remains to be explored. Whatever the mechanism, it is clear that addition to the diet of a greater amount of indigestible material would result in more bulky faeces and a fall in the observed percentage of faecal fat without affecting the total daily output of fat. If the average dry weight of faecal solids were increased from 10.5 to 16.9 g. per day by the addition of *non-fatty* residue in the diet, the percentage faecal fat of the cases in group C would drop from 30.2% to 18.8% and would then be well within the normally accepted limits. The daily output of fat would remain at 3.1 g. There are therefore good grounds for the belief that the cases of group C are *not* cases of steatorrhoea.

While these arguments and conclusions are strongly in favour of the determination of the daily fat excretion as the better criterion of a diagnosis of steatorrhoea (and this seems to be the generally accepted view), the determination of the percentage faecal fat of a random specimen is by no means a useless procedure.

Of the total of 47 cases of steatorrhoea in groups B and D, only one case had a percentage faecal fat less than 14%—the actual figure being 10.3% fat. This patient was passing an average of 54 g. of faecal solids per day. Therefore, if the percentage of faecal fat is less than 14% a state of steatorrhoea is most unlikely unless the faecal mass is abnormally bulky. If the

figure is less than 10% of the dry weight a diagnosis of steatorrhoea can be confidently excluded.

Of the 159 experiments in group A, the percentage faecal fat was less than 10% in 44 cases (27%). In those 44 cases a diagnosis of steatorrhoea could have been ruled out by the analysis of a random specimen of faeces, with the saving of a great amount of time and work both in the ward and in the laboratory. In a further 48 cases (30%) the percentage faecal fat lay between 10 and 14%, and in these, also, a diagnosis of steatorrhoea could have been excluded, with considerable confidence on the result of the analysis of a random specimen. Put in another way, 92 of the 231 fat balances carried out in this series (that is, 40%) were simply a waste of time.

Summary

The results of 231 fat balances in 138 patients suspected of having steatorrhoea have been critically examined. From a study of the literature it appears that any percentage faecal fat over 25%, or any daily excretion of fat greater than 5 g., is probably abnormal —the latter figure being more significant than the former. On this basis the 231 fat balances have been divided into four groups, and the significance of the findings of each group has been discussed.

The total weight of dry faecal material excreted per day is an important figure, and account must be taken of it when examining the results of any fat balance. It should also be recorded in the biochemical report.

All cases where the daily excretion of fat is abnormally high should be regarded as cases of steatorrhoea, irrespective of the percentage faecal fat. Cases where the percentage faecal fat is abnormally high but where the daily output of fat is within normal limits (that is, where the daily faecal mass is abnormally low) should not be diagnosed as steatorrhoea.

Chemical analysis of a random specimen of faeces is a very useful procedure in excluding a possible diagnosis of steatorrhoea. If the percentage faecal fat is less than 10% of the dry weight, steatorrhoea is excluded. If the value lies between 10 and 14% a diagnosis of steatorrhoea is most improbable unless the patient is also passing very bulky faeces. The great advantages of the analysis of a random specimen of faeces are (1) the saving of time and work both in the ward and in the laboratory, and (2) the fact that it can be successfully used as a screening test on out-patients.

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FREEZE-DRIED B.C.G. VACCINE

STABILITY OF THE VACCINE UNDER DIFFERENT CONDITIONS OF STORAGE AND PERSISTENCE OF TUBERCULIN SENSITIVITY IN SCHOOLCHILDREN AFTER VACCINATION

SECOND REPORT TO THE MEDICAL RESEARCH COUNCIL BY THEIR COMMITTEE ON THE STANDARDIZATION OF FREEZE-DRIED B.C.G. VACCINE*

During recent years freeze-dried B.C.G. vaccine has been developed in a number of countries. In Britain the vaccine is prepared by Glaxo Laboratories Ltd., and the method employed has been described by Ungar, Farmer, and Muggleton (1956). Freeze-dried B.C.G. vaccine has advantages over the liquid preparation in that it can be fully tested in the laboratory before it is issued for use, and its stability gives it a considerably longer life. It was decided, however, before using the vaccine extensively in this country to investigate the consistency of the viable count of a number of routinely prepared batches, and also to compare its ability to produce tuberculin sensitivity with that of the Danish liquid vaccine, which has now been shown to confer substantial protection against tuberculosis for at least six and a half years (Medical Research Council, 1956, 1959). A previous report, giving the results of a preliminary investigation (Medical Research Council, 1958), showed that the range of variation in viable count was no greater with the British dried vaccine than it was with the Danish liquid vaccine, and that the conversion rates produced by the batches of dried vaccine used in this study, although slightly less than with the liquid, were nevertheless satisfactory.

In the preliminary investigation, the dried vaccine used had been stored continuously in the refrigerator since its preparation, and it was found that periods of up to 10 months' storage did not affect its ability to produce a satisfactory conversion rate. It was considered important, however, to make further investigations, by both laboratory and clinical methods, of the stability of the vaccine at different temperatures and after different periods of storage in order to obtain information which would serve as a basis for recommendations relating to storage. It was also considered advisable to investigate the persistence of tuberculin sensitivity after vaccination. In the new studies, therefore, tuberculin tests were made both at one to

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for and at 10 to 13 months after vaccination. Additional information was also obtained by retesting for tuberculin sensitivity 9 to 13 months after vaccination those children who took part in the preliminary study.

Laboratory Tests of Stability

The determination of the number of viable bacillary particles (viable count) in both the dried and the liquid vaccine was made by the Medical Research Council's Biological Standards Control Laboratory, and the methods employed, which have been fully described by Osborn (1960), were similar to those used in the preliminary investigation (Medical Research Council, 1958). For each assay the average count was in most cases obtained from the results of separate tests on six 1-ml. ampoules. The liquid vaccine was also tested by the State Serum Institute, Copenhagen, and the results from both laboratories with the 12 batches used in the clinical trials are given in Table I. There was a good

TABLE I.—*Results of Determinations of Viable Counts of the Batches of Liquid B.C.G. Vaccine*

Batch No.	Viable Count in Millions/ml.	
	Results of M.R.C. Control Laboratory	Results of State Serum Institute
1276	31·1	28·5
1278	27·5	18·3
1279	20·8	19·8
1280	23·2	23·7
1282	25·3	18·2
1283	21·8	20·6
1284	9·7	14·7
1285	10·2	16·3
1286	24·3	21·9
1329	10·3	12·8
1332	10·8	16·5
1333	15·6	15·6

correlation between the two laboratories, the viable counts obtained by the Control Laboratory ranged from 9.7 to 31.1 $\times 10^6$/ml., with an average of 19.2 $\times 10^6$/ml., and those obtained from the State Serum Institute from 12.8 to 28.5 $\times 10^6$/ml., with an average of 18.9 $\times 10^6$/ml.

The stability of the dried vaccine at different temperatures was investigated in two separate studies. In each study the viable count of ampoules removed at intervals from storage in the refrigerator at 4° C. was compared with that of ampoules taken at the same time from storage at higher temperatures. The first study was made with five batches, ampoules from each being stored simultaneously at 4° C., room temperature (average 23° C.), and 37° C. for up to 63 weeks, and the second with four batches, each being stored simultaneously at temperatures between 4° C. and 45° C. for shorter periods. The reference batch, No. 125, which was used in the previous investigation, was also used throughout the present study and its viable count frequently determined during 115 weeks of storage at 4° C.

Stability of Freeze-dried Vaccine at 4° C. and Room Temperature

The results of the first study with batches Nos. 116, 117, 131, 133, and 145, together with those obtained with the reference vaccine No. 125, are shown in Fig. 1. From the time of preparation until the stability tests began, all batches were stored at 4° C. Only those results obtained with ampoules stored at 4° C. and room temperature are given in the figure, which shows the viable count in relation to the time at which the batches were prepared and also indicates the time at which they were used in the trials. In the case of batches 116, 131, 133, and 145, viable counts were also made with

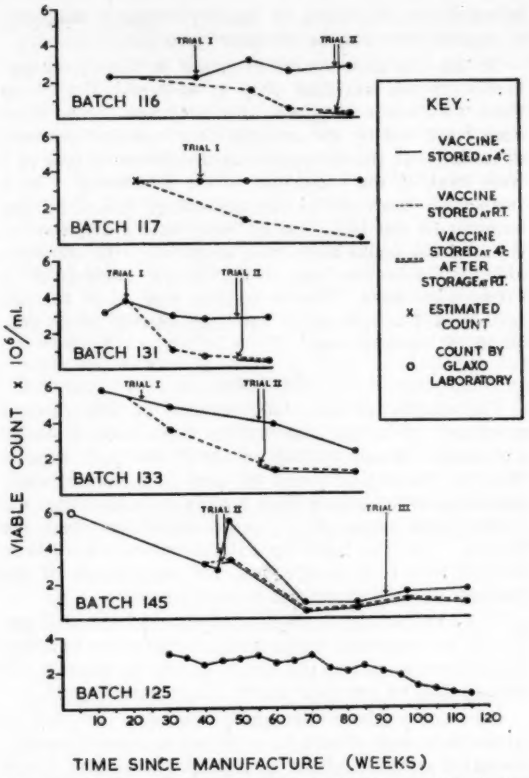

FIG. 1.—Viable count of freeze-dried B.C.G. vaccine during storage at 4° C. and 23° C. Times at which vaccines were used in the previous trial are indicated by "Trial I" and in the present trials by "Trial II" and "Trial III."

ampoules returned to 4° C. after they had been held at room temperature. The results obtained with ampoules stored at 37° C. were insufficent to be shown graphically and are given in Table II; it is interesting to note that with batches 131 and 133 there were still some viable particles present after storage at 37° C. for 39 and 41 weeks respectively.

TABLE II.—*Results of Tests of Viable Counts of Four Batches of Freeze-dried B.C.G. Vaccine Stored at 37° C.*

Batch No.	Viable Count ($\times 10^6$/ml.) at Beginning of Storage at 37° C.	Period of Storage at 37° C. (Weeks)	Viable Count
116	2·3	51	No colonies with undiluted vaccine
117	3·5	63	" " " " "
131	3·8	12	700/ml.
		21	30/ml.
		39	A few colonies with undiluted vaccine
133	5·8	12	40,000/ml.
		41	A few colonies with undiluted vaccine
		64	No colonies with undiluted vaccine

It is evident that the level of viable count of batches 116, 117, and 131, when stored at 4° C. remained approximately the same over the whole period of testing —namely, 65, 45, and 45 weeks respectively. With batch 133, stored at 4° C., there was a fall in viable count over the 70 weeks of testing, but it was less marked in comparison with that after storage at room temperature. Storage at room temperature of these four batches, however, resulted in a definite fall in

viable count amounting to approximately threefold to eightfold over a period of 30 to 60 weeks. The results of the tests with batch 145 suggest that this batch was less stable than the other four, a definite decline in viable count occurring both with the ampoules stored continuously at 4° C. and with those stored at room temperature for a period of one month before being returned to 4° C.

The results with the reference batch 125 are included in Fig. 1 for comparison; they show that the viable count remained fairly constant between 30 and 90 weeks from the time of preparation but that after this time there was a slight decline.

Stability of Freeze-dried Vaccine at Temperatures Between 4° C. and 45° C.

The results of the second study, with four batches Nos. 256, 262, 264, and 287, are shown in Fig. 2, which gives the viable count in relation to the time at which the tests were begun and not to the time at which the batches were prepared. With the three batches 256, 268, and 264, which were stored at 4° C., room temperature, 37° C., and 45° C., the results showed that the viable count was maintained at both 4° C. and room temperature over the whole of the six-week period, but that a rapid reduction occurred at 37° C. and 45° C. This reduction, which was evident from the tests made as early as 24 hours after storage, resulted in an exceptionally low viable count after 14 days at 37° C. and after two days at 45° C.

A more detailed examination of the fall in viable count at these higher temperatures was made with batch 287, over a shorter period of storage of 78 hours, with more frequent viable counts and four different temperatures of storage—namely, 4° C., 32° C., 37° C., and 45° C. The results again showed the rapid fall in count during the early period of storage at both 37° C. and 45° C. At 32° C., however, the viable counts were similar to those obtained at 4° C., no fall being evident over the 78-hour period.

Clinical Trials of Stability

General Plan

The investigations were made in the same six areas in Middlesex as before (Medical Research Council, 1958). In the main part of the study, 3,596 children aged 13 and 14 years were tuberculin-tested between October, 1957, and March, 1958. Those who were tuberculin-negative were given, according to an effectively random process, (*a*) the liquid vaccine, (*b*) the dried vaccine stored in the refrigerator throughout, or (*c*) the dried vaccine, from the same batch, stored for a period at room temperature. The vaccination sites were examined and tuberculin tests repeated one to four and 10 to 13 months after vaccination.

The liquid vaccine was drawn from the normal supply of 1-ml. ampoules received each week from Copenhagen for distribution to local health authorities in Britain. It was used within 11 days of issue and stored at refrigerator temperature between production and vaccination.

Four batches of the dried vaccine were used—Nos. 116, 131, 133, and 145—the first three having been used also in the previous trials. Each batch was divided into two parts: one part was stored continuously at refrigerator temperature between production and vaccination, and the other, after initial storage at refrigerator temperature, was held for a period at room temperature before use.

Tuberculin Sensitivity Before Vaccination

Each child was given the following examination. An intracutaneous tuberculin (Mantoux) test was made on the left forearm with 3 T.U., using 0.1 ml. of 1/3,000 old tuberculin,* and after 72 hours the greatest diameter of palpable induration was recorded. If there was no induration, or if the diameter was less than 5 mm., the reaction to 3 T.U. was regarded as negative and a second intracutaneous test was made on the same forearm with 100 T.U., using 0.1 ml. of 1/100 old tuberculin. The greatest diameter of induration to this second test was recorded, as before, after 72 hours, and children with no induration or an induration of less than 5 mm.

*The same batch of old tuberculin (international standard strength) was used as in the preliminary study.

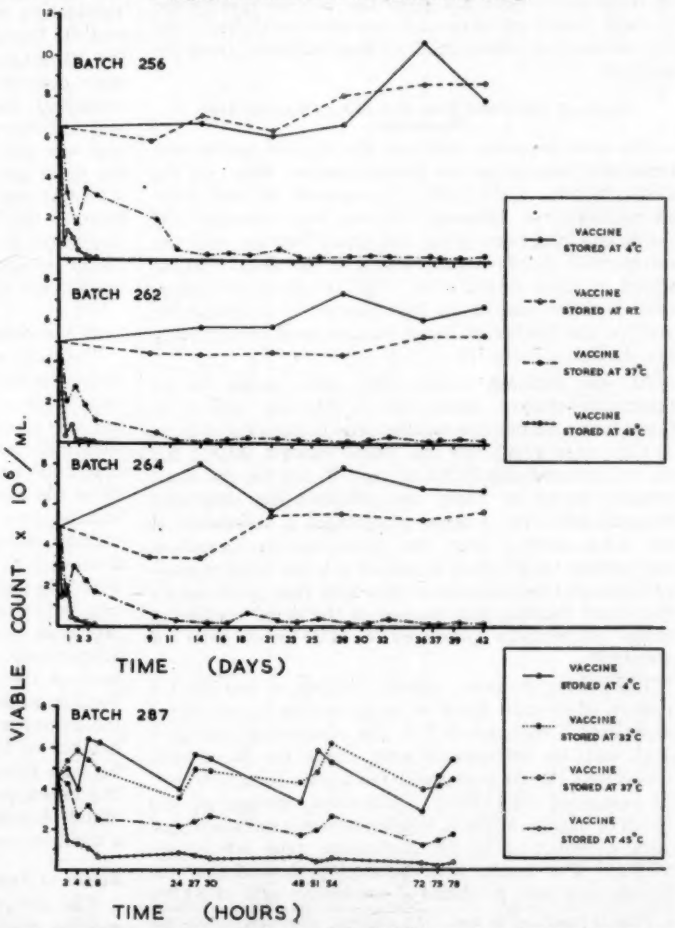

FIG. 2.—Viable counts of freeze-dried B.C.G. vaccine during storage at 4° C. to 45° C.

diameter were regarded as negative reactors to 100 T.U., and were included in the trials.

A total of 3,596 children completed the initial tuberculin tests; of these, 297 (8.3%) gave positive reactions to 3 T.U., and a further 641 (17.8%) reacted to 100 T.U. A total of 2,658 children (73.9%) were thus negative to 100 T.U.

Vaccination of Children

The tuberculin-negative children born in January, April, July, or October were given the liquid vaccine; those born in February, May, August, or November were given the dried vaccine stored throughout at refrigerator temperature; those born in the remaining four months were given the dried vaccine stored at room temperature. The dried vaccine was reconstituted by adding 1 ml. of sterile distilled water to each ampoule, drawing the suspension into a syringe and expelling it into the ampoule several times. The dose of both the dried and the liquid vaccine was 0.1 ml., given intracutaneously into the lower deltoid area of the left arm on the day that the result of the tuberculin test to 100 T.U. was recorded.

Of the 2,658 tuberculin-negative children, 2,642 were vaccinated, 891 receiving the liquid vaccine, 863 the refrigerated dried vaccine, and 888 receiving the dried vaccine stored at room temperature. Of the remaining 16 children, 15 were not given the vaccine appropriate to their month of birth and one was considered unfit for vaccination; these children were excluded from the analysis.

Results of Tuberculin Tests One to Four Months After Vaccination

The same procedure was used for the post-vaccination tuberculin tests as for the pre-vaccination tests. Of the 2,642 children, 1,950 (74%)† completed the first post-vaccination tests between one and four months. Of these, 668 had been given the liquid vaccine, 632 the refrigerated dried vaccine, and 650 the dried vaccine stored at room temperature. The results of the tuberculin tests for each of the four batches of dried vaccine and for the batches of liquid vaccine used concurrently are shown in Table III.

All the children except two were found to be tuberculin-sensitive either to 3 T.U. or 100 T.U. Considering all batches together, the conversion rates to 3 T.U. were 95.2% for the liquid vaccine, 85.3% for the refrigerated dried vaccine, and 77.5% for the dried vaccine stored at room temperature; the difference between any two of these percentages is significant at the 0.1% level. Thus the dried vaccine stored at refrigerator temperature produced a lower level of post-vaccination tuberculin sensitivity than that produced by the liquid vaccine, and storage of the dried vaccine at room temperature produced a still lower level of sensitivity.

There were, however, some variations in this general pattern when each batch of dried vaccine is considered separately. With batch 133, the conversion rate to 3 T.U. with the refrigerated part, stored for 14 months, was closely similar to that with the liquid vaccine—97.8% as compared with 100%. Moreover, storage of this batch of vaccine at room temperature was not associated with a reduction in the conversion rate, which was 97.7%. The results with batch 116 showed that the refrigerated part produced a conversion rate of 84.8% and the part stored at room temperature of 73.6% compared with a rate of 92.4% produced by the liquid vaccine. Thus, storage of batch 116 at room temperature was associated with a decline in tuberculin sensitivity. The findings with dried vaccine batch 131 were similar, a conversion rate of 86.6% being obtained for the refrigerated part, compared with 74.1% for the part stored at room temperature and with 93.9% for the liquid vaccine.

Batch 145, stored in the refrigerator, produced a conversion rate to 3 T.U. of 77.3% compared with that of 98.1% produced by the liquid vaccine, a difference which was much greater than those with the other batches of dried vaccine. There was little difference in the conversion rate of 75.6% produced by the part stored at room temperature, compared with that produced by the part stored in the refrigerator. The relatively low conversion rate produced by batch 145 occurred despite its high viable count at the time of use, and an attempt was made to clarify the problem by retesting the batch after a longer period of storage at refrigerator temperature. The results of this test are given below.

Diameter of Tuberculin Reactions One to Four Months After Vaccination

The degree of tuberculin sensitivity was measured by the diameter of induration produced by 3 T.U., after vaccination with the four batches of the dried vaccine and the liquid vaccine given concurrently. Fig. 3 shows the distribution of all reactions and Table III gives the mean diameter of the positive reactions. For all batches combined, the mean diameter of the positive reactions was 13.6 mm. for the children given the liquid vaccine, and was greater than those of 11.9 mm. and 11.7 mm. for those given the refrigerated dried vaccine and that stored at room temperature respectively; the differences between the first mean and each of the two latter are significant at the 0.1% level. A similar difference was found on comparing each batch of dried vaccine with the batches of liquid vaccine used concurrently.

Local Vaccination Lesions One to Four Months After Vaccination

The local vaccination lesions were examined and their diameters recorded at one to four months after vaccination, at the same time as the post-vaccination tuberculin test was given. The number of children examined was somewhat larger than the number who completed the tuberculin test. Local lesions were observed in all but 10 of the children, of whom two had been given liquid vaccine, four refrigerated dried vaccine, and four dried vaccine stored at room temperature. The mean diameters of the lesions were 9.5 mm. for 708 children who received the liquid vaccine, 8.3 mm. for 682 who received the refrigerated dried vaccine, and 8.4 mm. for 707 who received the dried vaccine stored at room temperature; the difference between the first value and each of the other two is significant at the 0.1% level. Similar differences were also apparent when comparing the lesions produced by each batch of the dried with the batches of liquid vaccine used concurrently. As may be seen from Fig. 4, the diameters of the majority of the lesions produced by all types of vaccine lay between 4 and 16 mm. There were no complications reported as a result of vaccination with any vaccine.

Results of Tuberculin Tests 10 to 13 Months After Vaccination

The results of the tuberculin tests made 10 to 13 months after vaccination are given in Table IV. Of the 2,642 children vaccinated, 1,752 (66%) completed

†This proportion is low; 354 children were deliberately not tested at this time since they were included in a separate investigation reported below.

the second post-vaccination tuberculin test between 10 and 13 months later; 594 had been given the liquid vaccine, 588 the refrigerated dried vaccine, and 570 the dried vaccine stored at room temperature; the majority had also been previously tested one to four months after vaccination. As before, almost every child, irrespective of the vaccine given, was tuberculin-positive to either 3 T.U. or 100 T.U.

Considering all batches together, the conversion rate to 3 T.U. for the liquid was 92.1%, for the refrigerated dried 85.0%, and for the dried vaccine stored at room temperature 79.8%. The differences between these values were a little less than the corresponding differences obtained at one to four months. They were nevertheless significant—the difference between the first value and the other two at the 0.1% level and between the second and third values at the 5% level. The results therefore support the conclusion reached as a result of the test at one to four months. When the results with each batch of dried vaccine were considered separately it was evident that the conversion rates produced by batches 116, 131, and 133 stored in the refrigerator were only slightly less than those produced by the liquid, while that produced by the refrigerated ampoules of batch 145 was much less than was produced by the liquid. It is also evident, as from the results at one to four months, that storage at room temperature reduced the activity of batches 116 and 131 but had no similar effect on batches 133 and 145.

The degree of tuberculin sensitivity, as measured by the diameter of induration produced by 3 T.U. 10 to 13 months after vaccination, is also shown in Table IV. Taking all batches together, the mean diameter of the positive reactions was 15.5 mm. for the liquid vaccine and greater than the values of 13.6 mm. for the refrigerated dried vaccine and 13.4 mm. for the dried vaccine stored at room temperature. The differences between the first value and each of the other two are significant at the 0.1% level.

TABLE III.—*Results of Tuberculin Tests in Children One to Four Months after Vaccination with (a) Liquid Vaccine, (b) Refrigerated Dried Vaccine, and (c) Dried Vaccine Stored at Room Temperature*

Batch No.	Liquid Vaccine					Refrigerated Dried Vaccine					Dried Vaccine Stored at Room Temperature				
	No. of Children Completing Tests	Positive to 3 T.U.		Negative to 3 T.U.		Mean Diameter of Positive Reactions to 3 T.U. (mm.)	No. of Children Completing Tests	Positive to 3 T.U.		Negative to 3 T.U.		Mean Diameter of Positive Reactions to 3 T.U. (mm.)	No. of Children Completing Tests	Positive to 3 T.U.		Negative to 3 T.U.		Mean Diameter of Positive Reactions to 3 T.U. (mm.)
		No.	%	Positive to 100 T.U.	Negative to 100 T.U.			No.	%	Positive to 100 T.U.	Negative to 100 T.U.			No.	%	Positive to 100 T.U.	Negative to 100 T.U.	
				No. %	No. %					No. %	No. %					No. %	No. %	
1280/2/3	197	182	92·4	15 7·6	0 0·0	13·6	158	134	84·8	24 15·2	0 0·0	11·3	182	134	73·6	47 25·8	1 0·5	11·1
1276/8/9	231	217	93·9	14 6·1	0 0·0	12·8	209	181	86·6	28 13·4	0 0·0	11·8	224	166	74·1	58 25·9	0 0·0	11·5
1282/3	86	86	100·0	0 0·0	0 0·0	13·0	93	91	97·8	2 2·2	0 0·0	12·3	88	86	97·7	2 2·3	0 0·0	12·4
1283/4	154	151	98·1	3 1·9	0 0·0	15·0	172	133	77·3	38 22·1	1 0·6	12·5	156	118	75·6	38 24·4	0 0·0	12·2
1284/5/6																		
All batches	668	636	95·2	32 4·8	0 0·0	13·6	All batches 632	539	85·3	92 14·6	1 0·1	11·9	All batches 650	504	77·5	145 22·3	1 0·2	11·7
Subsidiary study with batch 145																		
1329/32/33	211	211	100·0	0 0·0	0 0·0	16·9	145 244	219	89·8	25 10·2	0 0·0	14·5	Not tested					

TABLE IV.—*Results of Tuberculin Tests at 10 to 13 Months in Children Previously Tested at One to Four Months after Vaccination with (a) Liquid Vaccine, (b) Refrigerated Dried Vaccine, and (c) Dried Vaccine Stored at Room Temperature*

Batch No.	Liquid Vaccine						Refrigerated Dried Vaccine						Dried Vaccine Stored at Room Temperature					
	No. of Children Completing Tests	Positive to 3 T.U.		Negative to 3 T.U.		Mean Diameter of Positive Reactions to 3 T.U. (mm.)	No. of Children Completing Tests	Positive to 3 T.U.		Negative to 3 T.U.		Mean Diameter of Positive Reactions to 3 T.U. (mm.)	No. of Children Completing Tests	Positive to 3 T.U.		Negative to 3 T.U.		Mean Diameter of Positive Reactions to 3 T.U. (mm.)
		No.	%	Positive to 100 T.U.	Negative to 100 T.U.			No.	%	Positive to 100 T.U.	Negative to 100 T.U.			No.	%	Positive to 100 T.U.	Negative to 100 T.U.	
				No. %	No. %					No. %	No. %					No. %	No. %	
1280/2/3	182	165	90·7	17 9·3	0 0·0	16·6	156	136	87·2	19 12·2	1 0·6	13·6	166	129	77·7	36 21·7	1 0·6	13·1
1276/8/9	201	188	93·5	12 6·0	1 0·5	15·0	183	168	91·8	15 8·2	0 0·0	13·3	181	146	80·7	31 17·1	4 2·2	13·2
1282/3	76	73	96·1	3 3·9	0 0·0	13·6	90	84	93·3	6 6·7	0 0·0	13·7	80	77	96·3	3 3·8	0 0·0	13·2
1283/4	135	121	89·6	13 9·6	1 0·7	15·9	159	112	70·4	47 29·6	0 0·0	13·9	143	103	72·0	40 28·0	0 0·0	14·0
1284/5/6																		
All batches	594	547	92·1	45 7·6	2 0·3	15·5	All batches 588	500	85·0	87 14·8	1 0·2	13·6	All batches 570	455	79·8	110 19·3	5 0·9	13·4

Similar differences were found in comparing batches 116, 131, and 145 separately with the batches of liquid given concurrently, but with batch 133 the three values of the mean diameter of induration were very similar.

Further Comparison of Refrigerated Dried Vaccine Batch 145 and Liquid Vaccine

In this subsidiary trial, made at a later date, batch 145 had been stored for a longer period in the refrigerator. The same procedure as before was used, except that the dried vaccine stored at room temperature was not tested and tuberculin tests were made on only one occasion after a vaccination—namely, one to four months. A total of 774 children in one of the study areas completed the initial tests; of these, 72 (9.3%) were positive to 3 T.U. and a further 120 (15.5%) to 100 T.U. A total of 582 children were thus negative to 100 T.U. The allocation to the vaccinated groups was made according to the month of birth, children born in January, March, May, June, September, or November being given the liquid vaccine and those born in the remaining six months the dried vaccine. Of the 582 tuberculin-negative children, 577 were included in the analysis, 267 receiving the liquid and 310 the dried vaccine; the remaining five were not given the vaccine appropriate to their month of birth.

Of the 577 vaccinated children, 455 (79%) completed the tests, 211 having received the liquid and 244 the dried vaccine; the results are shown in Table III. All the children given the liquid vaccine were tuberculin-positive to 3 T.U. compared with 89.8% of those given the dried vaccine, and the mean diameters of the positive reactions were 16.9 mm. and 14.5 mm. respectively. It is thus evident that the difference between the conversion rate produced by batch 145 and by the liquid vaccine in this subsidiary trial was less than that obtained in the main trial despite the longer period of storage of the dried vaccine.

Relationship Between the Results of the Laboratory and Clinical Tests

Table V gives the conversion rates (taken from Tables III and IV) obtained in each post-vaccination test, together with the viable counts of both the liquid and the dried vaccine at the time they were used in the trials and the periods of storage of the dried vaccine.

It is evident that the three batches—116, 131, and 133—after being stored in the refrigerator for 19, 12, and 14 months respectively, produced a high degree of sensitivity both at one to four and at 10 to 13 months, the conversion rates being only slightly less than those obtained with the liquid vaccine. The viable counts of these three batches of dried vaccine at the time they were used were 2.9, 2.9, and 3.9×10^6/ml. respectively. Batch 145, however, was definitely less active, conversion rates of 77.3% at one to four months and 70.4% at 10 to 13 months being obtained in comparison with the corresponding figures for the liquid vaccine of 98.1 and 89.6%. It is not clear why batch 145 should have produced such a low conversion rate; the batch had been stored in the refrigerator for 10 months—a shorter period than for the others—and had a higher viable count—namely, 5.5×10^6/ml.—at the time it was used in children. These anomalous results may have been due to an ampoule-to-ampoule variation arising from the unstable nature of the batch, and, because of this, the viable count of the ampoules tested in the laboratory may not have been a true indication of the viable count of those used in the trial. Support for this suggestion was obtained from the results of a subsidiary trial made with batch 145 after 22 months' storage in the refrigerator. In this later trial the vaccine gave more satisfactory results than previously, producing a conversion rate to 3 T.U. of 89.8% compared with one of 100% produced by the liquid vaccine used concurrently. The viable count of the ampoules tested at this stage was 1.5×10^6/ml., and in this case was probably a true indication of the viable count of those used in the subsidiary trial.

When the results obtained with the dried vaccine stored at room temperature are considered it is seen that batches 116 and 131 produced lower conversion rates both at one to four and at 10 to 13 months than those produced by the refrigerated vaccine. The viable counts of the batches had fallen by the time of use—with batch 116 from 2.9 to 0.3×10^6/ml. after 12 months at room

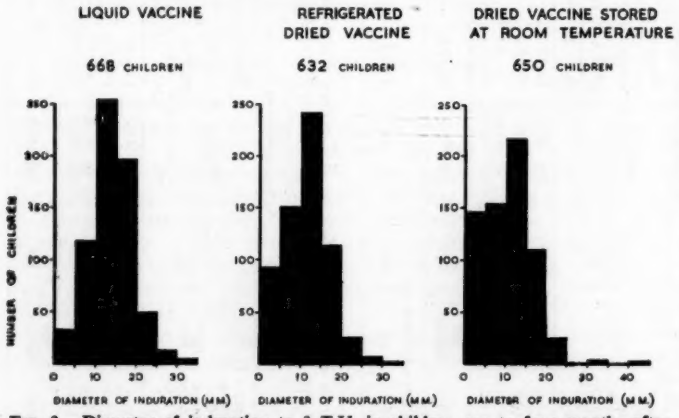

FIG. 3.—Diameter of induration to 3 T.U. in children one to four months after vaccination with (*a*) liquid vaccine, (*b*) refrigerated dried vaccine, and (*c*) dried vaccine stored at room temperature.

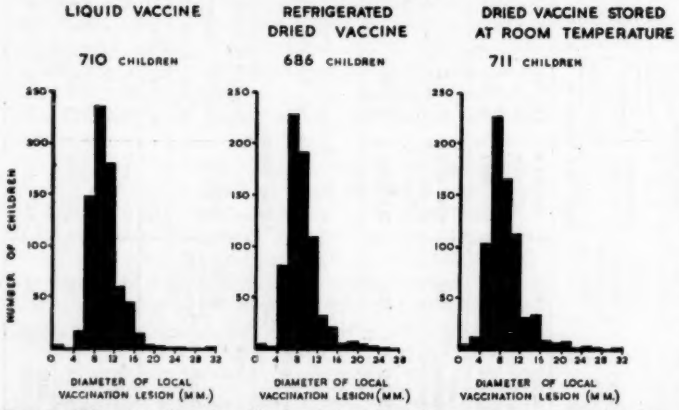

FIG. 4.—Diameter of local vaccination lesions in children one to four months after vaccination with (*a*) liquid vaccine, (*b*) refrigerated dried vaccine, and (*c*) dried vaccine stored at room temperature.

temperature and with batch 131 from 2.9 to 0.5×10^6/ml. after seven months at room temperature. Batch 133, on the other hand, showed no evidence of loss of activity during its storage at room temperature for nine months, producing as good a conversion rate as that produced by the refrigerated vaccine when tested both at one to four and 10 to 13 months—a result which was probably due to the fact that the decline in viable count during storage, from 3.9 to 1.4×10^6/ml., was not so great as that with batches 116 and 131. Ampoules of batch 145 were stored at room temperature for one month only and when tested gave a conversion rate similar to that given by the refrigerated vaccine.

The viable counts of the batches of liquid vaccine used are also given in Table V, but it is not possible to make a valid comparison between them and those of the dried vaccine since the two vaccines are manufactured by different processes producing dissimilar bacillary aggregates.

Persistence of Tuberculin Sensitivity after Vaccination

It is clear from the results given in Table V that in all tests with both the dried and the liquid vaccine there was no waning in the level of tuberculin sensitivity 10 to 13 months after vaccination. This was evident not only with those vaccines which gave good conversion at one to four months, but also with those which had lost activity on storage at room temperature and with batch 145, which, in the main trial, showed low activity both after storage in the refrigerator and after a period at room temperature.

TABLE V.—*Conversion Rates Produced by the Dried and the Liquid Vaccine, their Viable Counts, and the Periods of Storage of the Dried Vaccine*

Batch No.	Dried Vaccine: Refrigerated Throughout — Period of Storage in Refrigerator (Months)	Viable Count ($\times 10^6$/mL.) at Time of Use	Percentage of Children Positive to 3 T.U. — Months after Vaccination: 1 to 4	10 to 13	Dried Vaccine: Stored for a Period at Room Temperature — Period of Storage: Initially in Refrigerator (Months)	Subsequently at Room Temp. (Months)	Viable Count ($\times 10^6$/mL.) at Time of Use	Percentage of Children Positive to 3 T.U. — Months after Vaccination: 1 to 4	10 to 13	Liquid Vaccine: Range of Viable Count ($\times 10^6$/mL.)	Percentage of Children Positive to 3 T.U. — Months after Vaccination: 1 to 4	10 to 17
116	19	2·9	*84·8*	*87·2*	7	12	0·3	*73·6*	*77·7*	21·8–25·3	*92·4*	*90·3*
131	12	2·9	*86·6*	*91·8*	5	7	0·5	*74·1*	*80·7*	20·8–31·1	*93·9*	*93·5*
133	14	3·9	*97·8*	*93·3*	5	9	1·4	*97·7*	*96·3*	9·7–21·8	*100·0*	*96·1*
145	10	5·5	*77·3*	*70·4*	9	1	3·3	*75·6*	*72·0*	9·7–24·3	*98·1*	*89·6*
145 (Subsid. trial)	22	1·5	*89·8*	—	—	—	—	—	—	10·3–15·6	*100·0*	—

TABLE VI.—*Results of Tuberculin Tests in Children in the Preliminary Study One to Four and 9 to 13 Months after Vaccination with the Dried and the Liquid Vaccine*

Interval since Vaccination (Months)	Liquid Vaccine: Batch No.	No. of Children Completing Tests	Positive to 3 T.U. — No.	%	Negative to 3 T.U. Positive to 100 T.U. — No.	%	Mean Diameter of Positive Reactions to 3 T.U. (mm.)	Dried Vaccine: Batch No.	No. of Children Completing Tests	Positive to 3 T.U. — No.	%	Negative to 3 T.U. Positive to 100 T.U. — No.	%	Mean Diameter of Positive Reactions to 3 T.U. (mm.)
1–4	*1240/41*	260	254	*97·7*	6	*2·3*	11·7	*116*	216	186	*86·1*	30	*13·9*	10·1
9–13	*1240/41*	224	220	*98·2*	4	*1·8*	14·7	*116*	199	172	*86·4*	27	*13·6*	12·4
1–4	*1242/43*	392	375	*95·7*	17	*4·3*	11·1	*117*	350	312	*89·1*	38	*10·9*	10·0
9–13	*1242/43*	329	313	*95·1*	16	*4·9*	13·5	*117*	277	249	*89·9*	28	*10·1*	12·5
1–4	*1244/45 1247/49*	542	504	*93·0*	38	*7·0*	11·7	*131*	578	519	*89·8*	59	*10·2*	10·8
9–13	*1244/45 1247/49*	468	433	*92·5*	35	*7·5*	14·8	*131*	505	448	*88·7*	57	*11·3*	13·8
1–4	*1250/51 1257/60*	735	721	*98·1*	14	*1·9*	12·2	*133*	628	585	*93·2*	43	*6·8*	11·2
9–13	*1250/51 1257/60*	686	659	*96·1*	27	*3·9*	15·1	*133*	568	504	*88·7*	64	*11·3*	14·0
1–4	*All batches*	1,929	1,854	*96·1*	75	*3·9*	11·8	*All batches*	1,772	1,602	*90·4*	170	*9·6*	10·7
9–13		1,707	1,625	*95·2*	82	*4·8*	14·7		1,549	1,373	*88·6*	176	*11·4*	13·5

TABLE VII.—*Results of Tuberculin Tests 12 Months after Vaccination in Children (a) Not Previously Tested, and (b) Once Previously Tested*

Vaccine	Batch No.	Children Not Previously Tested: No. Completing Tests	Positive to 3 T.U. — No.	%	Negative to 3 T.U. Positive to 100 T.U. — No.	%	Mean Diameter of Positive Reactions to 3 T.U. (mm.)	Children Previously Tested at 6 to 8 Weeks: No. Completing Tests	Positive to 3 T.U. — No.	%	Negative to 3 T.U. Positive to 100 T.U. — No.	%	Mean Diameter of Positive Reactions to 3 T.U. (mm.)
Liquid vaccine	1280	27	27	*100·0*	0	*0·0*	13·9	25	23	*92·0*	2	*8·0*	14·6
	1285	69	57	*82·6*	12	*17·4*	11·6	49	44	*89·8*	5	*10·2*	13·5
Refrigerated dried vaccine	116	22	18	*81·8*	4	*18·2*	9·9	27	25	*92·6*	2	*7·4*	10·6
	145	57	39	*68·5*	18	*31·6*	11·5	71	44	*62·0*	27	*38·0*	11·7
Dried vaccine stored at room temperature	116	18	13	*72·2*	5	*27·8*	12·8	29	24	*82·8*	5	*11·2*	11·0
	145	45	29	*64·4*	16	*35·6*	11·1	51	34	*66·7*	17	*33·3*	12·3
All batches		238	183	*76·9*	55	*23·1*	11·7	252	194	*77·0*	58	*23·0*	12·3

A similar result was obtained when the children who took part in the preliminary study (Medical Research Council, 1958) were tested for tuberculin sensitivity 9 to 13 months after vaccination. The tests were made with 1,707 (76%) of those who had received the liquid vaccine and 1,549 (also 76%) of those who had received the dried vaccine. The results are given in Table VI, and for comparison those obtained previously at one to four months are also included. It is seen that the conversion rates obtained at 9 to 13 months were strikingly similar to those at one to four months for each of the dried vaccines and for the liquid vaccines used concurrently, although with both types of vaccine the mean diameter of the positive reactions to 3 T.U. was slightly less at one to four than at 9 to 13 months.

These results indicated that the dried vaccine was able to produce a level of tuberculin sensitivity which was maintained for 9 to 13 months as well as that produced by the liquid vaccine. It was nevertheless considered advisable, in view of the fact that sensitivity after vaccination may be affected by repeated tuberculin tests (Magnus and Edwards, 1955), to determine whether the first post-vaccination tuberculin test might have influenced the results of the second test. A separate study was made in one of the study areas with some of the vaccinated children from the main trial. They were divided into two groups, those born in January, March, May, July, September, or November being chosen for tuberculin-testing at both one to two and at 12 months after vaccination and those born in the alternate months at 12 months only.

Of 354 vaccinated children chosen for tuberculin-testing on the two occasions after vaccination 238 (67%) completed both tests, and of 336 chosen for tuberculin-testing at one year only, 252 (75%) completed the test. The vaccines used in this study were two batches of liquid, two batches of dried stored continuously in the refrigerator, and the same two batches of dried held for a period at room temperature. The results are given in Table VII.

Considering all vaccines together, the conversion rates at 12 months to 3 T.U. were 76.9% in the group of children tested at 12 months only and 77.0% in the group tested both at one to two and at 12 months; the difference is not significant. When the batches are considered separately, although there is a wide range of conversion rates, there is again no significant difference between those in the two groups, either with each individual batch or with each type of vaccine. These results are supported by those showing the degree of tuberculin sensitivity as measured by the diameter of induration produced by 3 T.U. at 12 months. For all vaccines together, the mean diameter of the positive reactions was 11.7 mm. for those receiving one tuberculin test and 12.3 mm. for those receiving two; the difference is not significant. Nor is there any significant difference when the results with each batch or type of vaccine are considered separately.

It may therefore be concluded that the results of the second post-vaccination tuberculin test at 12 months were not influenced by the earlier one at one to two months and that the results obtained in the other studies were a true indication of persistence of tuberculin sensitivity as a result of vaccination.

Conclusions

It is evident from the results of this and the previous investigation that the British freeze-dried B.C.G. vaccine may be regarded as satisfactory for use as a successful prophylactic against tuberculosis since it was shown to produce, in strictly controlled trials in tuberculin-negative adolescent children, a high degree of tuberculin sensitivity which developed at a similar rate and was maintained to the same extent as that produced by the Danish liquid vaccine.

Care must be taken, however, in the handling of the dried vaccine during storage and transit. The vaccine gave adequate conversion rates after a period of storage at 4° C. of up to one year from its preparation. Storage at 23° C. for approximately six months, on the other hand, was associated with a definite decline in activity, although the conversion rates obtained with such vaccines were, nevertheless, within the range which was found in trials with liquid vaccine to be associated with a substantial degree of protection against tuberculosis (Medical Research Council, 1956, 1959). However, from the results of both the laboratory and the clinical studies it would seem advisable not to store the dried vaccine at temperatures greater than 4° C., although a temperature of approximately 20° C. for short periods of up to a week, which may be required for transit in temperate zones, would be unlikely to cause much deterioration. The laboratory tests showed that the dried vaccine was extremely unstable at 37° C. and, although in one test one of the batches maintained its viable count for three days at 32° C., it would seem undesirable—at least until more information is available—to expose the vaccine to temperatures greater than that recommended above, even for short periods.

The results obtained with one of the batches of dried vaccine suggest that all batches may not have the same degree of stability. It may therefore be advisable before issuing the dried vaccine for clinical use to subject it to accelerated degradation tests, similar to the kind used with dried smallpox vaccine (World Health Organization, 1959) in order to eliminate those batches of low stability. Such a test is under investigation.

Although these investigations were not designed to obtain evidence of the correlation between the activity of the dried vaccines in children and their viable counts, the results do suggest that batches with viable counts of more than 1×10^8/ml. produce adequate tuberculin sensitivity. The batches which are being generally used in this country at the present time have counts ranging from 4 to 7×10^8/ml., and those which have been tested in regular clinical studies have been shown to produce in adolescent children a high degree of tuberculin sensitivity and an exceptionally low incidence of untoward vaccination reactions.

The Medical Research Council's Committee on the Standardization of Freeze-dried B.C.G. Vaccine wishes to thank Dr. J. Ungar and his colleagues, of Glaxo Laboratories Ltd., and Dr. K. Tolderlund and his colleagues, of the State Serum Institute, Copenhagen, for their co-operation in this investigation. Thanks are also due to Glaxo Laboratories Ltd. for the supply of freeze-dried B.C.G. vaccine.

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EFFECT OF PROLONGED TREATMENT WITH HYPOTENSIVE DRUGS ON RENAL FUNCTION IN HYPERTENSION

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Changes in the renal circulation in most subjects with essential hypertension long precede impairment of renal function (Goldring and Chasis, 1944). Early changes consist of a moderate reduction in effective renal blood-flow (E.R.B.F.) and of a smaller fall in glomeruiar filtration rate (G.F.R.). Later, E.R.B.F. and G.F.R. fall further, and it is recognized (Goldring and Chasis, 1944) that if the disease enters a malignant phase, although G.F.R. and E.R.B.F. may be only moderately reduced in the early stages, rapid reduction is the usual course, with extremely low values in the final stages. We have confirmed these observations, and our values in three normal subjects and in patients with benign essential and malignant hypertension are shown in Fig. 1.

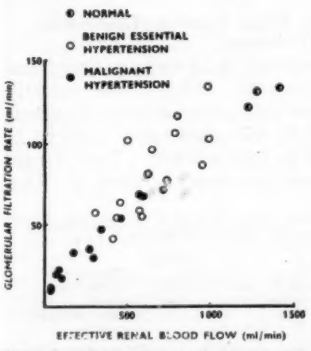

FIG. 1.—Comparison of glomerular filtration rate and effective renal blood-flow in three normal subjects and patients with benign and malignant hypertension.

The immediate effect of ganglion-blocking drugs on the renal circulation of hypertensive patients is to produce a sharp fall in E.R.B.F. and G.F.R. (Mackinnon, 1952; Grob *et al.*, 1953; Moyer and Mills, 1953), and this is associated with reduced urine-flow (Mackinnon, 1954). These changes are, however, short-lived, and a return to the original levels occurs despite continued reduction of blood-pressure (Grob *et al.*, 1953; Moyer and Mills, 1953; Mackinnon, 1954). In view of this acute effect of ganglion-blocking drugs it seemed possible that prolonged administration might affect renal function adversely, though it was hoped that continued reduction of blood-pressure might halt progressive vascular changes or even induce reversal of such changes, particularly in the malignant phase of hypertension.

We report here observations on renal function and the renal circulation in hypertensive subjects during prolonged treatment with hypotensive drugs.

Material and Methods

All the cases described were thought to have severe hypertensive disease requiring treatment. Indications for treatment were as follows: (1) malignant phase of hypertension with grade IV retinopathy (Wagener and Keith, 1939) (8 patients); (2) severe benign essential hypertension (7 patients, 4 with grade III retinopathy) (Wagener and Keith, 1939).

In all patients the diastolic blood-pressure after rest in hospital was 120 mm. Hg or more, and in most it was 130 mm. Hg or more. All patients had either electrocardiographic or radiological evidence of left ventricular enlargement, and most had both.

Patients were admitted to hospital for assessment, and renal clearances were carried out after a period of rest before hypotensive treatment was given. Treatment was started in all patients with a small subcutaneous dose of hexamethonium bromide (C6). This was given at eight-hourly intervals to patients without elevation of the blood urea but less often and in smaller doses if this was present. Frequent blood-pressure measurements were made, and the dose of C6 was increased as tolerance was acquired. The final dose of C6 varied from 105 to 570 mg. daily (average 218 mg.). While in hospital patients were taught to give their own injections, and continued to do so after discharge. Patients were also given hydrallazine hydrochloride ("apresoline") 50–100 mg. by mouth two hours after each injection. Subsequently, when they became available, subcutaneous or oral pentolinium tartrate ("ansolysen") was substituted for C6 in three patients and mecamylamine ("inversine") in five, and the blood-pressure was restabilized. "Rauwiloid and veriloid" (4 tablets daily) was substituted for hydrallazine in 11 patients and chlorothiazide ("saluric") 1 g. daily in one.

After stabilization on hypotensive drugs patients were discharged from hospital and seen regularly in the out-patient clinic for adjustment of the dose of drugs. They were readmitted for subsequent renal clearances during treatment. G.F.R. and E.R.B.F. were measured by the determination of inulin and *p*-aminohippurate (P.A.H.) clearances respectively, using the method of Smith *et al.* (1938). Inulin and P.A.H. were estimated by the technique of Dick and Davies (1949), and each clearance figure cited represents the mean of two consecutive clearance periods, each of 20 minutes' duration. Frequent estimations of the blood urea were performed during the early stages of treatment.

Results

Control of Hypertension.—An attempt was made to reduce the standing diastolic blood-pressure to 100 mm. Hg or below in each case four hours after the last dose of the ganglion-blocking drug. This was achieved in most patients with careful adjustment of the dose as tolerance to the ganglion-blocking drug was acquired. In patients in whom the blood urea was initially elevated smaller doses of the drugs were used and we were satisfied with smaller reductions in blood-pressure. We felt that the best control possible with the drugs available at the time had been obtained short of producing severe side-effects. Papilloedema subsided in all patients with malignant hypertension who survived long enough (within two months), and retinal haemorrhages and exudates resolved when present. The electrocardiogram became normal or improved in most patients. Symptoms were usually strikingly improved, particularly headache and vision, which was often severely impaired before treatment in patients with malignant hypertension.

Renal Function: Malignant Hypertension (8 Patients)

Patients with Azotaemia.—There were four patients in whom the blood urea was elevated before treatment was given. The actual levels at this time were 109, 108, 105, and 88 mg./100 ml. G.F.R. (12 and 22 ml./min.) and E.R.B.F. (45 and 92 ml./min.) were extremely low

in the two patients in whom renal clearances were performed. Clearances were repeated in one of these (R. K.) after three months' treatment but showed no significant change. This patient died of uraemia after 10 months. Two patients survived for 10 months and during this time lost their severe symptoms. Vision improved remarkably in both. In each of them the elevated blood urea rose further during the first week of treatment but subsequently fell to the original level in one and slightly

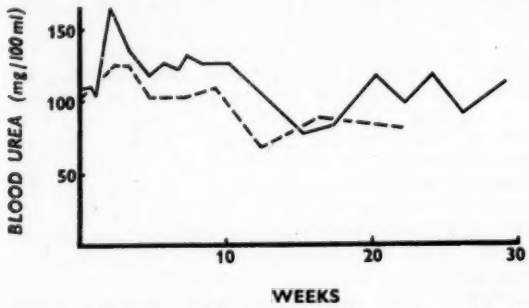

FIG. 2.—Blood-urea levels in two patients with malignant hypertension during satisfactory blood-pressure reduction with hypotensive drugs.

below this in the other (Fig. 2). In spite of satisfactory control of the hypertension the blood urea did not rise again until shortly before death, when in both patients it rose abruptly. In one patient with chronic pyelonephritis and malignant hypertension the blood-pressure fell precipitously when very small doses of C6 were given. There was an associated increase in blood urea, which later fell as the blood-pressure rose after withdrawal of treatment (Fig. 3). This patient was subsequently treated with hydrallazine hydrochloride alone, but the hypertension was not adequately controlled, and she died of uraemia after three months. The fourth patient survived only one month after treatment was started, the blood urea rising steadily to 350 mg./100 ml. before death.

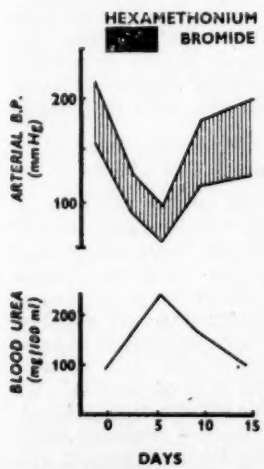

FIG. 3.—Increase in azotaemia due to excessive blood-pressure reduction in patient with malignant hypertension.

Patients Without Azotaemia.—There were four patients with malignant hypertension in whom the blood urea was normal before treatment. E.R.B.F. was severely impaired in three and moderately reduced in the fourth. G.F.R. was severely reduced in one patient and moderately reduced in the remaining three. The changes in renal clearances occurring during treatment are shown in Table I. Two patients showed a moderate fall in both G.F.R. and E.R.B.F. after just over two years' and six years' treatment respectively. In two patients clearances were unchanged after treatment for one month (this patient died of uraemia after two and a half years' treatment, clearances not being repeated) and over six years respectively.

TABLE I.—*Changes in G.F.R. and E.R.B.F. in Patients with Malignant Hypertension During Prolonged Treatment*

Case	Sex	G.F.R. (ml./min.)	E.R.B.F. (ml./min.)	Duration of Treatment	Remarks
G.J.	F	68	589	Before treatment	Died cerebral haemorrhage
		87	593	8 months	
		64	489	18 ,,	
		55	447	26 ,,	
A.R.	M	69	563	Before treatment	,, ,,
		73	590	14 months	
		43	318	6 years 2 months	
G.G.*	M	47	344	Before treatment	Alive and well
		61	404	2 months	
		70	493	5 ,,	
		46	374	5 years 1 month	
L.R.	M	71	705	Before treatment	Died uraemia after 31 months
		74	600	1 month	
R.K.	M	12	45	Before treatment	Died uraemia after 10 months
		7	53	3 months	

* This patient also had chronic glomerulonephritis.

In two patients a transient rise in blood urea to 60 mg./100 ml. occurred during the first week of treatment, the level subsequently falling to normal without interruption of treatment. Three of these patients have died at intervals of two years two months (cerebral haemorrhage), two years seven months (uraemia), and six years two months (cerebral haemorrhage) after starting treatment. The remaining patient is alive and well after over six years' treatment.

Renal Function: Severe Benign Essential Hypertension (7 Patients)

The blood urea was normal in all these patients, and remained so during treatment. E.R.B.F. was severely reduced in four and moderately reduced in three patients before treatment. G.F.R. was moderately reduced in three and more severely in four patients. The changes occurring during treatment are shown in Table II. One

TABLE II.—*Changes in G.F.R. and E.R.B.F. in Patients with Benign Essential Hypertension During Prolonged Treatment*

Case	Sex	G.F.R. (ml./min.)	E.R.B.F. (ml./min.)	Duration of Treatment
J.C.	M	87	956	Before treatment
		117	993	16 months
H.W.	M	96	650	Before treatment
		78	643	15 months
		77	374	6 years 6 months
G.J.	F	54	446	Before treatment
		30	242	5 years 7 months
J.S.	M	64	461	Before treatment
		59	494	10 months
M.W.	F	62	475	Before treatment
		70	446	5 years
W.J.	M	59	535	Before treatment
		67	476	5 years
D.B.	F	86	807	Before treatment
		92	568	5 years

patient treated for 10 months showed no change either in E.R.B.F. or G.F.R. One patient treated for 16 months showed an increase in G.F.R. to normal but no significant change in E.R.B.F. Of the remaining five patients who were treated for over five years, G.F.R. was unchanged in three but fell in two. E.R.B.F. was unchanged in one, but fell in four, though the change in one was slight. One patient died after a myocardial infarction after two years' treatment, five patients are alive and well after over five years' treatment, and in one treatment was withdrawn (at the patient's request) after 10 months.

Discussion

The four patients with malignant hypertension and azotaemia before treatment all died of renal failure within 10 months, nevertheless it was felt that life had

been prolonged and symptoms temporarily relieved in two of these. Two patients with malignant hypertension without azotaemia survived for over two years and two for over five years, but although only one of these died of renal failure, renal clearances fell in two of the others. Thus in patients with malignant hypertension further impairment of the renal circulation was prevented in only one patient—a man with chronic glomerulonephritis who was alive and well after treatment for more than five years. His renal clearances initially improved but subsequently returned to the original levels. This is interesting in view of the evidence of Harington *et al.* (1959) that the survival rate of treated patients with malignant renal hypertension is better than those with malignant essential hypertension.

Five patients with benign essential hypertension were treated for five years or longer. Renal clearances showed no significant changes in two and definite deterioration in three. In two patients treated for shorter periods (10 months and 16 months) E.R.B.F. showed no significant change. G.F.R. rose to normal in one patient.

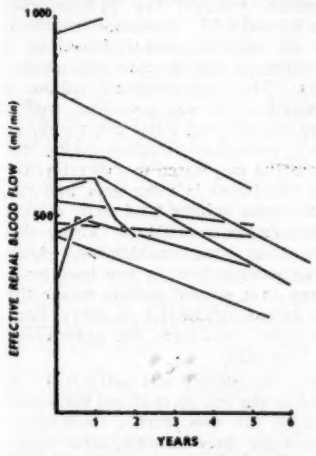

FIG. 4.—Changes occurring in effective renal blood-flow during prolonged treatment with hypotensive drugs.

In the patients without azotaemia there is no indication that blood-pressure reduction for prolonged periods with ganglion-blocking drugs contributed to the reduced renal clearances. In fact, the clearances in all patients in whom they were repeated within 1 to 14 months after starting treatment showed no significant fall (Fig. 4), and it was only later that reduction occurred. This suggests that further impairment of the renal circulation occurred in the natural course of the disease rather than as a result of treatment. It is possible, however, for increasing azotaemia to result from blood-pressure reduction in patients in whom renal failure is already apparent (Fig. 3), and in one patient with malignant hypertension and azotaemia steadily increasing uraemia culminating in death within one month occurred in spite of satisfactory control of the hypertension. It seems possible that reduction of the blood-pressure in this patient contributed to the increasing uraemia. Transient increase in the blood urea during the first week of treatment occurred in two patients. A similar occurrence has been reported previously (Harington *et al.*, 1959) and was thought by these authors to be due to extrarenal factors. In spite of this, it is often possible in patients with azotaemia, by very careful blood-pressure reduction, to control symptoms for a time without resulting increase in blood urea (Fig. 2; Smirk and Alstad, 1951; Harington and Rosenheim, 1954; Abrahams and Wilson, 1957).

From our results there is no evidence that prolonged treatment was responsible for deterioration in renal function—a similar conclusion to that reached by Abrahams and Wilson (1957) in patients with hypertension secondary to chronic renal disease. There is a suggestion that it may have slowed down the rate of deterioration, for in one patient with malignant hypertension and in four patients with benign hypertension, two of whom were treated for over five years, no deterioration occurred in clearance values whereas without treatment further deterioration might have been expected. It seems, however, that once changes have occurred in the renal circulation of hypertensive subjects they are not reversible by present methods of treatment, for renal clearances did not improve in any patient treated for a prolonged period. It may be possible in some patients to arrest the changes, but in most there is continued deterioration. This may be due to the inability to maintain the blood-pressure at normal levels throughout the 24 hours with the drugs available at the time this study was made, for there is no doubt that our patients remained hypertensive during a considerable proportion of the day and night. The more efficient and more easily controlled hypotensive drugs now available may be more effective in preventing continued renal vascular changes.

Harington *et al.* (1959) have clearly shown that treatment of malignant hypertension improves the expectation of life, but they have also stressed the prognostic significance of renal function before treatment. Prognosis remains extremely poor in these patients, and the aim must always be for earlier diagnosis and treatment before renal changes become severe; for hypotensive drugs are of little use in the later stages of renal failure.

Summary and Conclusions

Observations on renal function have been made in eight patients with malignant hypertension and seven patients with severe benign essential hypertension during prolonged treatment with hypotensive drugs.

Four patients with malignant hypertension and azotaemia died of renal failure within 10 months.

Two patients with malignant hypertension without azotaemia showed deterioration in renal clearances during treatment lasting two years and five years respectively, and one patient died of renal failure (renal clearances were not performed after one month's treatment). Renal clearances were unchanged in one patient with malignant hypertension and chronic glomerulonephritis after five years' treatment. Of the remaining five patients who were treated for over five years, G.F.R. rose slightly in three (the change is probably not significant) but fell in two.

Renal clearances did not improve in any patient treated for over five years, but G.F.R. returned to normal in one patient treated for 16 months. There was no evidence that prolonged treatment with hypotensive drugs affected renal function adversely, though the greatest care is necessary in avoiding excessive blood-pressure reduction in patients with severely impaired renal function. Prognosis in such patients is still extremely poor and the necessity for early diagnosis and treatment of malignant hypertension is stressed.

It was found that prolonged treatment with hypotensive drugs did not cause further impairment of the renal circulation in hypertensive subjects. Slow deterioration in renal clearances occurred in most patients during treatment, but this was thought to be the result of natural progression of the disease, possibly as a result of inability to maintain normal blood-pressure through the 24 hours

with present methods of treatment. In some patients renal-clearance values remained unchanged, and it was thought that further deterioration in these patients may have been prevented by hypotensive treatment.

We are grateful to Professor C. H. Stuart-Harris for advice during the preparation of this paper and for allowing us to investigate and treat patients under his care. We are indebted to Dr. R. Ollerenshaw, of the department of medical illustration, Manchester Royal Infirmary, for the figures.

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HYPERALDOSTERONISM

REPORT OF A CASE

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The syndrome of hyperaldosteronism is now being recognized with increasing frequency. The clinical picture is characterized by polyuria and polydipsia in addition to hypertension. The case reported here is of interest in that polyuria was absent and observations on the patient suggest a possible mechanism for the polyuria of this syndrome.

Case History

An assistant production manager aged 28 had previously enjoyed perfect health. When first seen in April, 1959, his sole complaint was some recent loss of visual acuity, noticed only while playing tennis. This led him to consult an optician, who referred him to hospital as a case of hypertensive retinopathy. On direct questioning he admitted to some recent tiredness but strenuously denied any polyuria, nocturia, or thirst. A routine medical examination in 1955 had shown a "high normal blood-pressure." There was no family history of hypertension.

On examination he appeared fit and active, with normal muscular power. His blood-pressure was 190/130. Both fundi showed haemorrhages, exudates, and arterial narrowing but no papilloedema.

Investigations.—A chest *x*-ray film showed slight cardiac enlargement and an E.C.G. showed left ventricular preponderance. The blood urea varied from 24 to 39 mg./100 ml. and the creatinine clearance was 90 ml./min. After 5 units of "pitressin" the urinary specific gravity rose to 1018. Urinary catechol amines were 90 μg./24 hours. The plasma electrolytes showed a consistently abnormal pattern of hypokalaemia and alkalosis. There were seven pre-operative measurements of potassium, with a mean of 3.1 mEq/l. (range 2.8 to 3.4 mEq/l.), and six measurements of bicarbonate, with a mean of 35.6 mEq/l. (range 33 to 38 mEq/l.). This suggested the possibility of an aldosterone-secreting tumour of the adrenal cortex, and a search was made to demonstrate a tumour but with negative results. Intravenous pyelogram, aortogram, and presacral insufflation of oxygen failed to show any abnormality.

Aldosterone and Electrolyte Excretion.—The sodium intake was varied to assess changes in aldosterone excretion and the patient's ability to get into sodium balance. The Chart shows the results of these investigations. When the sodium intake was 110 mEq/day the aldosterone excretion varied between 24 and 76 μg./day (normal values 4 to 15 μg./day on free sodium intake); the 24-hour-urine volume was then between 1.9 and 2.3 l. Reduction in sodium intake to approximately 10 mEq/day was followed by a sharp fall in sodium excretion, so that the new balance was established in three days. This was achieved without a change in aldosterone excretion but was associated with a marked reduction in urine volume (and water consumption). There was some decrease in potassium excretion during this time. When the sodium intake was raised to 210 mEq/day a new balance was again established in three days, and this time there was a rise in the urine volume (and water intake) but no depression of aldosterone excretion. During this period the potassium excretion rose considerably. After the operation, when all replacement therapy had been withdrawn and the patient was on a normal sodium intake the aldosterone excretion was extremely low (1.4 μg./day). Four months later, under the same conditions, the aldosterone excretion was 1.3 and 1.2 μg./day.

Operation.—On June 8 a laparotomy was performed. A small tumour was palpated in the left adrenal and the whole gland was removed. During this procedure cardiac arrest occurred, requiring massage for three minutes, after which ventricular fibrillation began. After one shock with the defibrillator normal rhythm was restored.

Histology.—The tumour was a spherical cortical adenoma 10 mm. in diameter. The histology showed cells with an eosinophilic cytoplasm like those of the zona reticularis, but a few were filled with lipoid. In places the cells showed a tubular formation with a clearly defined fibrous stroma.

Post-operative Course.—During the first two days the patient was mentally confused, but after this his mental and intellectual functions appeared to be completely normal. The blood-pressure remained at pre-operative levels for three days and then gradually fell, and by the fourteenth day was down to 140/90. A week after operation the plasma potassium had risen to 4.6 mEq/l. and the bicarbonate was then 35 mEq/l. Three days later the potassium was 5.0 mEq/l. and the bicarbonate 31 mEq/l.

Subsequent Course.—The blood-pressure has remained at normal levels since operation, the average pressure four months after being 140/90. However, although the blood-pressure and plasma electrolytes remained normal, the blood urea rose to 50 mg./100 ml. a month after the operation, confirmed on two occasions. This was interpreted as indicating renal damage, and he was readmitted in September for reassessment. This time the creatinine clearance was 130 ml./min., and after pitressin the urinary specific gravity rose to 1022. The blood urea during this stay in hospital varied between 26 and 43 mg./100 ml. A renal biopsy was attempted but no tissue was obtained. However, the white-cell excretion in the urine after an artificially induced fever did not rise outside normal limits and all urinary cultures were sterile, so there appeared to be no evidence of chronic pyelonephritis. Ten months after operation the blood-

pressure was 130/85, plasma potassium 3.7 mEq/l., plasma bicarbonate 29 mEq/l., and blood urea 37 mg./100 ml.

Discussion

The diagnosis of hyperaldosteronism was suggested by the finding of hypertension, hypokalaemia, and alkalosis. The urinary *p*H was between 6.7 and 7.2, as has been previously reported in this condition (Milne *et al.*, 1957). The high aldosterone excretion, which was not depressed by salt-loading, confirmed the diagnosis. It is of great interest that this patient was able to achieve sodium balance very rapidly both on a low-salt intake and on a high one, despite the unchanged aldosterone excretion. That patients with excess aldosterone of endogenous or exogenous origin can escape from the sodium-retaining effect of the hormone is well known. This "escape mechanism" has been studied by August *et al.* (1958) and involves changes in water turnover (Mills and Robinson, 1960). The results presented here show that when sodium is restricted the water turnover decreases and the polyuria disappears. In this patient the polyuria was surprisingly absent as a symptom, although the urine volume was about 2 litres. Obviously the presence or absence of polyuria depends upon the patient's level of salt intake.

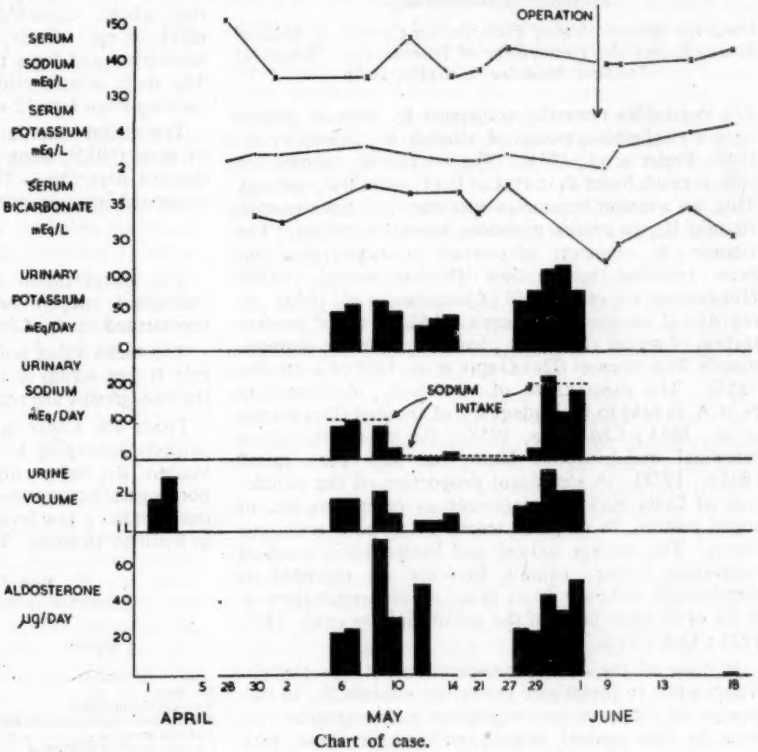

Chart of case.

The high-sodium intake caused considerable loss of potassium, and this was probably an important factor in producing the low serum potassium found on the day after operation. The cardiac arrest during the operation might have been related to this, and obviously potassium repletion should have been more energetic in the pre-operative period.

After operation, aldosterone excretion fell to very low levels and remained so when he was reinvestigated four months later. It appears that these patients may be in a position similar to those with Cushing's syndrome due to an adenoma. It is well known that after removal of such an adenoma it may be many months before endogenous A.C.T.H. production returns. It seems that the hormone controlling aldosterone secretion is also slow to return after removal of an adenoma. This apparently causes the patients surprisingly little disturbance. This patient was in sodium balance on a normal salt intake when aldosterone excretion was just over 1 µg./day. However, at this time, in spite of having a creatinine clearance of 130 ml./min., his blood urea was 50 mg./100 ml. It seems reasonable to assume that he attained sodium balance by a mechanism the reverse of the "escape mechanism." This probably involves excessive reabsorption of fluid in the proximal tubule, as appears to happen also in cirrhotics with ascites (Schedl and Bartter, 1958), and this may cause excessive reabsorption of urea.

Some of the apparent decrease in renal function which occurs after removal of aldosterone-secreting tumours might be explained by this mechanism.

Summary

A case of hyperaldosteronism with hypertension but without polyuria or polydipsia is reported. In spite of a continued high level of aldosterone excretion the patient was able to attain sodium balance on a varying intake. This was accompanied by alteration in the urinary volume. Removal of the tumour resulted in a cure of the hypertension.

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The new British Standard for Peters' aural specula (B.S. 3259 : 1960) provides requirements for the size of the conical joint for fitting the specula to the mount, the size range of specula, and essential features relating to the lens. The purpose of this standard is primarily to ensure interchangeability of specula fittings on the mount of the body of the instrument, and to provide a uniform size designation. The power of the lens has been specified; otherwise materials and general details of design have been left to individual choice. Price 3s. (postage extra to non-subscribers) from the Sales Branch, British Standards Institution, 2, Park Street, London, W.1.

SERUM VITAMIN B_{12} IN VEGETARIANS

BY

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The vegetables normally consumed by man in general have a negligible amount of vitamin B_{12} (Lewis *et al.*, 1949; Peeler *et al.*, 1951). The vitamin B_{12} content of milk is much lower than that of liver, meat, fish, and egg. Thus an average vegetarian diet may not have enough vitamin B_{12} to ensure optimum human nutrition. The vitamin B_{12} content of serum in vegetarians has been reported to be low (Wokes *et al.*, 1955; Dhopeshwarkar *et al.*, 1956; Chatterjea *et al.*, 1959). In nutritional macrocytic anaemia (N.M.A.) a low concentration of serum vitamin B_{12} has been found in approximately 50% of cases (Das Gupta *et al.*, 1955; Chatterjea, 1958). The main cause of vitamin-B_{12} deficiency in N.M.A. is held to be inadequacy of the diet (Das Gupta *et al.*, 1953; Chatterjea, 1958); the possibility of an intestinal malabsorptive factor has also been raised (Baker, 1958). A significant proportion of the population of India may be categorized as vegetarian, due to social custom, to religious tenets, or to poor economic status. The average red-cell and haemoglobin levels of vegetarian Indians cannot, however, be regarded as significantly different from those of non-vegetarians in India or in other parts of the world (Sokhey *et al.*, 1937, 1938; Das Gupta, 1949).

In view of the above considerations, it was thought worth while to investigate the serum vitamin B_{12} in two groups of subjects—non-vegetarian and vegetarian—as seen in the general population and in those with haematological disorders.

Material and Method

The present communication deals with observations on 232 subjects, consisting of 61 normal persons, 67 with tropical eosinophilia, 39 with N.M.A., 35 with aplastic anaemia, and 30 with chronic myeloid leukaemia. The distribution of non-vegetarians and vegetarians is shown in the Tables.

Subjects belonging to the vegetarian group were taking rice, wheat, vegetables, pulses, and milk, but no fish, meat, or egg. Each one of them had been taking the vegetarian diet for a period varying from 5 to 25 years. The daily consumption of milk was in general small, varying from 6 to 12 oz. (170 to 340 ml.) per head.

The serum vitamin B_{12} was estimated by the method of Ross (1952), using *Euglena gracilis* var. *bacillaris* as the test organism. The total vitamin B_{12} content was expressed in micromicrograms per millilitre.

Results

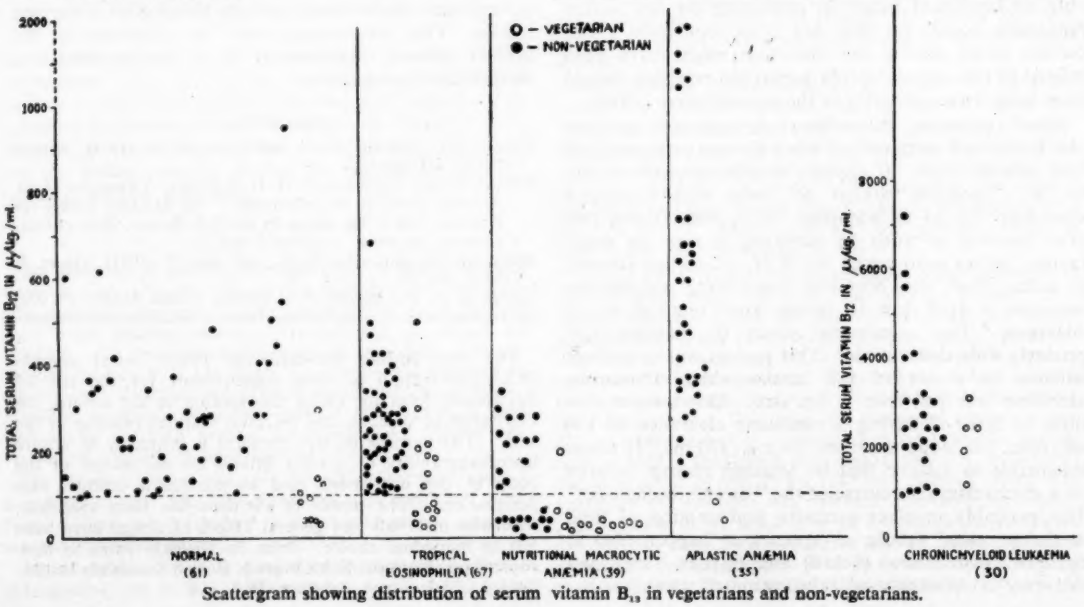
The concentration of total serum vitamin B_{12} in each individual subject belonging to the two groups is represented in the Chart.

The mean value and range of variation of total vitamin B_{12} of serum in the different subjects belonging to the two groups are recorded in Tables I and II.

From the Chart it is seen that six of the normal subjects belonging to the vegetarian group had serum vitamin B_{12} values lower than the lowest value in the non-vegetarian group—that is, 98 $\mu\mu$g./ml. In tropical eosinophilia a low level of serum vitamin B_{12} was found in 8 out of 16 cases. In nutritional macrocytic anaemia,

TABLE I.—*Non-vegetarian*

Subjects	No. of Cases	Total Vitamin B_{12} in $\mu\mu$g./ml. of Serum	
		Range	Mean ±S.E.
Normal	51	98 to 940	281·9 ± 22·7
Tropical eosinophilia	51	100 to 670	254·8 ± 16·1
Nutritional macrocytic anaemia	26	0 to 330	136·9 ± 20·7
Aplastic anaemia	33	144 to 1,800	621·9 ± 76·6
Chronic myeloid leukaemia	25	960 to 7,200	2,754·0 ±317·2



Scattergram showing distribution of serum vitamin B_{12} in vegetarians and non-vegetarians.

TABLE II.—*Vegetarian*

	No. of Cases	Total Vitamin B_{12} in $\mu\mu$g./ml. of Serum		Cases with <98 $\mu\mu$g./ml. Vitamin B_{12}
		Range	Mean ± S.E.	
Normal	10	36 to 290	92·3 ± 24·3	60%
Tropical eosinophilia	16	20 to 490	139·5 ± 30·6	50%
Nutritional macrocytic anaemia	13	20 to 196	47·5 ± 12·7	92·3%
Aplastic anaemia	2	40 and 80	—	Low in both the cases
Chronic myeloid leukaemia	5	1,190 to 3,100	2,219 ±318·8	0

a low serum vitamin B_{12} value was found in all the vegetarians except one. Of the aplastic anaemia patients only two were vegetarians, and in both of them the serum vitamin B_{12} was low, being 40 and 80 $\mu\mu$g./ml. respectively. No differential pattern was seen in chronic myeloid leukaemia, all the subjects showing elevated level.

A comparative study of Tables I and II shows that in the vegetarians the mean values were significantly lower than those in non-vegetarians in all groups except chronic myeloid leukaemia. In the vegetarians the percentage of cases having a serum vitamin B_{12} level lower than 98 $\mu\mu$g./ml. was 92.3% in N.M.A., 60% in normals, and 50% in tropical eosinophilia.

Discussion

Results of the present investigation indicate that the vegetarians have a serum vitamin B_{12} concentration which is significantly lower than that in the non-vegetarians. On the basis of clinical evaluation and analysis of dietary habits, vitamin B_{12} deficiency in the vegetarians appears to be dietary in origin. In a parallel study with ^{60}Co-labelled vitamin B_{12} for investigating the pathogenesis of vitamin B_{12} deficiency in N.M.A., dietary inadequacy appeared to be more important than the factor of intestinal malabsorption (Banerjee *et al.*, 1959).

In normal subjects and the cases of tropical eosinophilia there was no significant anaemia or macrocytosis. The blood picture in vegetarians and non-vegetarians was more or less similar, though their serum vitamin B_{12} levels were different. Some of the vegetarians followed for one or two years did not show any decline of haemoglobin or R.B.C. level in spite of the serum vitamin B_{12} level continuing to be low. These findings are not in complete agreement with those of Wokes *et al.* (1955), who found evidence of anaemia and macrocytosis in a significant proportion of vegans investigated by them. It must, however, be remembered that, owing to the exclusion of milk and milk products from their food, the average diet of a vegan was relatively more deficient in vitamin B_{12} than that of a normal Indian vegetarian. Maintenance of normal haemoglobin and R.B.C. values with a serum vitamin B_{12} value as low at 40 $\mu\mu$g./ml. poses certain questions of fundamental importance. Mollin and Ross (1952) observed that a serum level of 100 $\mu\mu$g./ml. was the critical concentration below which signs of vitamin B_{12} deficiency could be recognized. They confirmed their observation later by stating that early megaloblastic change was noticed in the bone-marrow of pernicious anaemia (P.A.) patients a few days after the serum vitamin B_{12} level had fallen below 100 $\mu\mu$g./ml.; at levels greater than this, the marrow remained normoblastic (Mollin and Ross, 1953).

In the present series the bone-marrow was normoblastic in tropical eosinophilia and aplastic anaemia. Bone-marrow examination was not done in normal subjects. Hence it is not possible to state whether they had any sign of vitamin B_{12} deficiency in the marrow. Repeated examination of peripheral blood did not, however, show any evidence of erythrocytic macrocytosis or granulocytic abnormality. In N.M.A. the bone-marrow was, however, found to be megaloblastic. It must be pointed out that, in N.M.A., megaloblastic bone-marrow was also seen in all the cases with high serum vitamin B_{12} (see Chart), suggesting that in this disease there is no direct correlation between serum vitamin B_{12} and bone-marrow changes. It is well known that N.M.A. as seen in the eastern part of India represents deficiency of folic acid and/or vitamin B_{12} (Das Gupta *et al.*, 1953; Chatterjea, 1958). The lack of correlation between serum vitamin B_{12} and bone-marrow changes in N.M.A. may therefore be explained on the basis of associated folic-acid deficiency, the degree of which cannot be ascertained from the serum vitamin B_{12} level.

In none of the cases with low serum vitamin B_{12}, including those of N.M.A., was there any neurological complications. This observation also was not in complete agreement with that of Wokes *et al.* (1955), who recorded neurological symptoms and signs in some of their subjects. In a few Indians with classical Addisonian pernicious anaemia subacute combined degeneration has, however, been found (Das Gupta and Chatterjea, 1951). In N.M.A. and in malabsorption syndrome neurological complications are conspicuous by their absence, though the serum vitamin B_{12} level in many cases may be as low as in pernicious anaemia. The main difference between P.A. and N.M.A. (or malabsorption syndrome) is with reference to intrinsic factor and neurological complications. In the present series all the vegetarians with low serum vitamin B_{12} had presumably no deficiency of intrinsic factor. Thus the circumstantial evidence becomes very strong in favour of intrinsic factor having some role, direct or indirect, in protecting the nervous system. If vitamin B_{12} *per se* was responsible for the protection of the nervous system, absence or rarity of neurological signs in N.M.A., in malabsorption syndrome, and in the present series of vegetarians cannot be satisfactorily explained.

It is possible that vitamin B_{12} absorbed from a system with an adequate amount of intrinsic factor (as in vegetarians, and in patients with N.M.A. and malabsorption syndrome) may be qualitatively different from vitamin B_{12} absorbed from a system grossly deficient in intrinsic factor (as in P.A.). Concentration for concentration, the former vitamin B_{12} may be more protective to the nervous system than the latter. The efficacy of parenteral vitamin B_{12} therapy in correcting the neurological complication of P.A. may be explained by assuming that the vitamin B_{12} as used in therapeutics is similar to the former but perhaps different from the latter. An alternative explanation would be the suggestion that therapeutically administered vitamin B_{12} is "activated" by extragastric sources of vitamin B_{12} (Callender and Lajtha, 1951). The above facts would tend to indicate that intrinsic factor, in addition to its role as promoter of absorption, may have an activating or maturing influence on vitamin B_{12}. Adequacy of intrinsic factor would ensure not only absorption but also activation or maturation of whatever small amount of vitamin B_{12} may be available to the system due to dietary inadequacy and/or intestinal malabsorption (Chatterjea, 1960).

An elevated level of serum vitamin B_{12} in chronic myeloid leukaemia, first reported by Beard *et al.* (1954), has been conclusively confirmed by a number of investigators. The exact cause of this elevated level is not clear. Lack of any differential pattern in the two groups—vegetarian or non-vegetarian—as revealed in the present study, indicates that in this disease the factor responsible for hypervitaminosis far outweighs the hypovitaminic effect of a vegetarian diet.

Summary

The serum vitamin B_{12} level was studied in 232 subjects (196 non-vegetarians and 46 vegetarians). The subjects belonged to the following five categories: normal, tropical eosinophilia, nutritional macrocytic anaemia, aplastic anaemia, and chronic myeloid leukaemia.

Serum vitamin B_{12} in the vegetarian group was, in general, lower than that in the non-vegetarian group. Chronic myeloid leukaemia was an exception, all the patients in this category showing a raised level as previously reported.

Low serum vitamin B_{12} was not, however, associated with any anaemia or neurological complications. The implications of these findings are discussed.

We are indebted to Dr. R. N. Chaudhuri, Director, School of Tropical Medicine, Calcutta, for providing necessary facilities for the study. We are grateful to Mr. S. K. Ghosh and Dr. Sandhya Ghose, of the department of haematology, for their help.

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The Italian Olympic Medical Committee is conducting a statistical study of competitors who took part in the Olympic Games in order to discover the correlations between medical characteristics and performance. To obtain this comprehensive medical data—in all, 78 medical characteristics for each athlete—for at least 2,000 of the 7,000 competitors in this year's games, the medical sections of various national Olympic Committees (including the German, Italian, and Russian) have agreed to supply the results of medical examinations of their athletes carried out in their own countries. Once this information has been collected it will be recorded on punched-cards which will then be processed by the IBM 305 RAMAC computer.

TREATMENT OF RESPIRATORY INFECTION IN SCHOOLBOYS WITH PHENETHICILLIN

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The administration of penicillin to children has hitherto presented several practical problems. Crystalline penicillin by injection gives satisfactory blood levels, but is painful and very unpopular with young patients. Oral penicillins G and V are far more acceptable, but the blood levels obtained are much lower than those achieved by parenteral administration, and are indeed often insufficient for satisfactory therapeutic effect. When phenethicillin (6-(α-phenoxypropionamido)penicillanic acid) was marketed as "broxil," it was claimed that this preparation would give blood levels at least equal to those after intramuscular injection of corresponding doses of penicillin G. Knudsen and Rolinson (1959) investigated the absorption and excretion of phenethicillin in adults, and their results confirmed this claim. Garrod (1960) compared the antibacterial activity of phenethicillin, penicillin G, and penicillin V. He found that, weight for weight, phenethicillin was more active than penicillin V or G against resistant staphylococci, and very slightly less active against streptococci and pneumococci.

In February, 1960, an outbreak of severe pharyngitis, with some complications, occurred among schoolboys aged 7–13 at Summer Fields Preparatory School, Oxford. The school is residential, and it was essential to deal promptly with the infection, which spread in a few days to 31 boys. Table I shows the incidence of the various types of infection. Most of the boys had severe pharyngitis and cervical lymphadenopathy. The illness ran much the same course both in those infected with β-haemolytic streptococci group A and in those from whom other organisms (*Str. pneumoniae, Str. viridans,* neisseria) were isolated. Fourteen boys had complications. One boy had uncomplicated lobar pneumonia and one had cellulitis of a finger.

TABLE I.—*Clinical Diagnosis and Treatment*

Condition	No.	Dose of Phenethicillin	Duration of Fever (Hours)	Failure
Pharyngitis due to β-haemolytic streptococci	13	12–250 mg. q.d.s. 1–500 ,, ,,	10–24 2–48	—
As above+otitis media ..	3	250 mg. q.d.s.	24	—
Pharyngitis due to other organisms	2	250 ,, ,,	1–24 1–48	—
As above+otitis media ..	2	250 ,, ,,	48	—
Pharyngitis+bronchitis (2 β-haemolytic streptococci)	5	2–500 mg. q.d.s 3–250 ,, ,,	4–24 1–48	—
Pharyngitis+sinusitis ..	4	3–500 ,, ,, 1–250 ,, ,,	3–48	2, resistant staphs
Lobar pneumonia	1	250 mg. q.d.s.	73, with initial dramatic fall	
Cellulitis of finger	1	250 ,, ,,	24	—

Methods

The boys were all treated with phenethicillin. The standard dose was 250 mg. (one tablet) four-hourly

during the day. In almost all cases there was a 12-hour interval during the night when no treatment was given. This dose was regarded as adequate for boys weighing 4½–7 st. (28.6–44.5 kg.). A few very big boys weighing 7–9 st. (44.5–57.2 kg.), and some with complications, were given 500 mg. q.d.s. Treatment was continued for five days in uncomplicated cases of pharyngitis, and for a week or 10 days in those with complications. The treatment was stopped in two cases (see Table I).

Blood for penicillin levels was taken once from each boy during treatment. The intervals between the previous dose of phenethicillin and venepuncture varied from 10 to 310 minutes. The concentration of antibiotic in the blood was determined by the tube-dilution method, using the Oxford H staphylococcus, and standard solutions of penicillin G and phenethicillin for comparison. The control solutions of penicillin G and phenethicillin gave identical results in every case.

TABLE II.—*Penicillin Levels in Blood*

Case No.	Age (Years)	Weight		No. of Doses of Phenethicillin Before Bleeding	Interval Between Previous Dose and Bleeding (Minutes)	Blood Penicillin (μg./ml.)
		lb.	kg.			
1	8	64	29·0	9	10	4
2	11	89	40·4	13	25	4
3	10	70	31·8	9*	30	2
4	11	71	32·2	17	40	2
5	12	81	36·7	5	40	4
6	8	66	29·9	5	50	8
7	12	106	48·1	9	65	4
8	9	71	32·2	7*	70	8
9	10	75	34·0	9	75	4
10	10	79	35·8	2	78	4
11	9	72	32·7	9	80	8
12	10	70	31·8	9	85	8
13	11	60	27·2	7	100	16
14	10	98	44·5	4	105	4
15	10	87	39·5	4*	108	16
16	10	66	29·9	4	185	2
17	9	67	30·4	4	190	1
18	12	110	49·9	3	195	0
19	9	63	28·6	4	220	1
20	8	62	28·1	4	220	0·25
21	11	66	29·9	4	230	0·5
22	8	64	29·0	4*	230	0·5
23	12	95	43·1	12	255	1
24	12	91	41·3	4	255	0·5
25	11	90	40·8	16	265	0
26	10	75	34·0	16	270	0·12
27	9	82	37·2	4	285	0
28	13	84	38·1	6	290	0
29	9	100	45·4	6	295	0
30	11	85	38·6	2	300	0
31	10	68	30·8	4	310	0

*These doses were 500 mg. All other doses were 250 mg. up till the time the blood was taken.

Results

The results are recorded in Table II, from which it will be seen that the blood level rises rapidly after taking the tablets, and drops again between three and four hours to very low or undetectable levels, regardless of the number of doses previously given. The absorption is obviously rapid, and the blood levels attained are comparable with those of penicillin G injected parenterally.

The clinical response to phenethicillin was very satisfactory. The patients with uncomplicated pharyngitis were afebrile and asymptomatic within 48 hours. The boy with lobar pneumonia responded as well as one would have expected had he been treated with penicillin by injection. The other complications cleared quickly (see Table I), except the cases of sinusitis. Three boys were afebrile within 48 hours, and symptoms settled after a further few days. Three boys did not respond to phenethicillin in a dose of 250 mg. four-hourly, and in two the fever remained high in spite of increasing the dose to 500 mg. q.d.s. From both, penicillin-resistant staphylococci were isolated, and they made rapid recovery when treated with erythromycin and tetracycline respectively. Few objections were raised by any of the boys to the new drug. The prospect of not having to have injections (of which several boys had had previous experience) overshadowed the discomfort of one venepuncture for estimation of the blood penicillin level.

Side-effects.—Two boys complained of nausea soon after taking the tablets on an empty stomach, but this passed off after a few days. Three boys had diarrhoea; in two it was very mild, and in one who was receiving 500 mg. q.d.s. it was fairly severe, but it stopped when the dose was halved. In every case the diarrhoea ceased when the course of tablets was completed. One child was lethargic while receiving phenethicillin, but this ceased after treatment.

Summary

In a residential preparatory school an outbreak of severe pharyngitis affected 31 boys, 14 of whom had some complications. Group A β-haemolytic streptococci were isolated from most of the patients. All patients were treated with phenethicillin, and the clinical results were satisfactory. Blood levels of penicillin during therapy were equivalent to those expected from parenteral administration of penicillin G. Phenethicillin was rapidly absorbed, and concentrations up to 16 μg./ml. were obtained. The concentration fell to very low levels after four and a half hours.

We thank Miss N. Lovett, S.R.N., matron of Summer Fields School, for her valuable assistance, and we are grateful to Beecham Research Laboratories, Ltd., for the supplies of "broxil" used in this study.

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A TRIAL OF A NEW MONOAMINE OXIDASE INHIBITOR IN ANGINA PECTORIS

BY

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Dramatic relief of angina pectoris with iproniazid (1-*iso*nicotinyl-2-*iso*propylhydrazine; "marsilid") was reported by Cesarman (1957). Other early reports were also favourable (Cossio, 1958; Towers and Wood, 1958). The serious risk of liver necrosis from iproniazid later became recognized (*New Engl. J. Med.*, 1958), and recent double-blind trials have shown no improvement of angina (Dewar *et al.*, 1959; Snow and Anderson, 1959; Fife *et al.*, 1960). Iproniazid inhibits monoamine oxidase, and the alleged effect on anginal pain was ascribed to this action. As early enthusiasm for iproniazid has waned, other monoamine inhibitors have been tried in angina, and we here describe a double-blind trial of one of them.

1-Pivaloyl-2-benzylhydrazine ("tersavid") is chemically related to iproniazid. Animal experiments have shown equally powerful inhibition of monoamine oxidase, but it is less toxic than iproniazid. Relief of angina has been reported in preliminary trials.

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Method of Trial

Twenty patients (2 women and 18 men) took part in the trial. Their mean age was 59.5 years (range 46–70 years). All had typical severe angina due to coronary artery disease, constant in degree for at least two months before the trial. Aortic stenosis was also present in two patients, rheumatic aortic incompetence in one, and mitral stenosis in one. The electrocardiogram was abnormal in 16 patients, with evidence of infarction in eight and of ischaemia in the remaining eight. Eleven patients were previously receiving anticoagulants and continued them throughout the trial.

A double-blind cross-over technique was used, each patient acting as his own control. The 20 patients were allocated to two equal groups by a random method. One group took tersavid for a month followed by identical inert tablets for a second month, and the other group took inert tablets followed by tersavid. No other alteration of treatment was made during the period of the trial. At the start of the tersavid period treatment was begun with 150 mg. daily. If there was no improvement in angina after one week, the dose was increased to 250 mg. daily and continued at this level for the next three weeks. The dose of inert tablets was similarly increased if angina continued unchanged after one week of the control period. The patients were seen at fortnightly intervals throughout the trial, when the severity of angina and the number of trinitrin tablets required were recorded. Weight, blood-pressure, evidence of fluid retention, and side-effects were also noted. An electrocardiogram was taken and serum glutamic-oxaloacetic and glutamic-pyruvic transaminase levels were estimated at monthly intervals.

Results

One patient, a man on anticoagulant treatment, died of recurrent myocardial infarction after three days on control tablets. Of the remaining 19 patients, only the one man with aortic incompetence reported improvement in angina with tersavid and no benefit from the inert tablets. Seven patients improved during both trial periods, and in the remaining 11 patients there was no significant change in angina. Three patients had associated intermittent claudication. In one of these—the one patient who reported benefit from tersavid—leg pain also decreased. The other two patients found no change in angina or leg pain.

No side-effects occurred apart from slight dizziness in two patients. There was no change in weight or blood-pressure, and no evidence of fluid retention. The electrocardiograms were also unchanged, and the transaminase levels remained normal.

Discussion

There is real need for a drug capable of producing prolonged relief of angina. The most widely prescribed remedy, pentaerythritol tetranitrate (P.E.T.N.), we have recently tried in high dosage on a double-blind basis with negative results. Twelve patients with angina received 60 mg. of P.E.T.N. three times daily for a month and identical inert tablets for another month. None found improvement on P.E.T.N. and not on control tablets. Similar negative results were reported by Dewar *et al.* (1959).

Recent experience with iproniazid is disappointing, and it may be doubted whether other monoamine oxidase inhibitors will relieve angina if iproniazid does not. The present trial, in which only 1 out of 19 patients improved while on tersavid and not during the control period, does not indicate that this drug is valuable in angina. However, in a recent trial of β-phenylisopropylhydrazine ("cavodil") (MacKinnon *et al.*, 1960) our experience has been less encouraging. Hepatic damage, with jaundice, developed in one of the 12 patients treated with it.

Summary

A monoamine oxidase inhibitor, tersavid, has been tried on a double-blind basis in 19 patients with angina. Only one patient appeared to benefit.

We are grateful to Dr. Horace Joules and Dr. Keith Ball for help with this trial. The tersavid and control tablets were kindly supplied by Roche Products Ltd.

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Medical Memoranda

Megimated Barbiturates

Partly owing to the wider prescription of barbiturates the mortality and morbidity from overdosage, accidental or suicidal, has risen considerably over the last decade. We are faced with a serious problem: 2,800 hospital cases of barbiturate poisoning were treated in 1949 and 6,000 in 1958. We can, with reasonable certainty, expect an even greater rise over the years ahead. There are two alternatives to combat this rise: either to stop using barbiturates or to safeguard their use. Some measures have, of course, already been taken to control their prescription and use. However, something more is needed, since the number of deaths continues to rise despite these statutory measures.

Attempts have been made to make barbiturates less dangerous by combining them with emetics and stimulants. These combinations appear to have had little success in practice. Following the work on bemegride ("megimide") by Shaw and his co-workers in 1954, over 200 articles appeared on its use in the treatment of barbiturate overdosage. These articles provided confirmation of the effectiveness of bemegride as a functional barbiturate antagonist. It seemed possible, therefore, that a combination of bemegride with barbiturates might lower the potential toxicity of overdosage from barbiturates. Trautner *et al.* (1957) and Gershon and Shaw (1957) were able to show that 10–20% bemegride with barbiturate in tablet form reduced or even prevented the development of coma or of prolonged sleep in doses of up to 2.6 g. of barbiturate. Quite naturally the critical test of whether this combination is effective in preventing death due to gross overdosage can never be performed

deliberately. Further data on its efficiency at very high dose levels has therefore had to be awaited.

First indications promised vindication of the belief upon which the "megimated barbiturates" were founded. Thus Skinner (1960) reported a case in which 50 "phenaglate" capsules (quinalbarbitone sodium 50 mg., phenobarbitone 25 mg., bemegride 7.5 mg.) had been taken with no resultant coma or respiratory depression. Heffernan (1959) reported a case in which 24 capsules were taken without any ill effect. Two similar cases have been reported to one of us personally in which "mylomide" (amylobarbitone 100 mg., bemegride 10 mg.) was taken in overdosage. In one case 25 tablets were taken, the stimulant effect of the bemegride being prominent, since after a number of hours of light sleep the patient awoke feeling excited. In the second case at least 16 tablets were taken; the patient was in light coma, but there was no respiratory depression.

Despite these earlier encouraging reports, a note of caution must now be introduced because of the occurrence of a death caused by the ingestion of a large amount of phenaglate.

CASE REPORT

The patient was a man aged 39. He was single, a clerk by profession, although he had been away from work for two weeks previous to his first admission to hospital, which was on April 9, 1957.

He had enjoyed fairly good health before and there was no history of psychiatric disorder in his family. The condition leading to his admission began towards the end of March, 1957, when he felt anxious and worried about an unhappy love affair. His anxiety became more acute, until on April 8, he attempted suicide by coal gas.

In hospital he was found to be acutely anxious and tense though he was not overtly depressed. To overcome the anxiety and tension he was sedated with amylobarbitone sodium, 1 gr. (65 mg.) t.d.s. No other treatment was given. On this regime he improved gradually, and was apparently well enough for discharge on May 25. Five days later he again attempted suicide with coal gas. He was readmitted to hospital, and, because he was thought to be depressed, was treated with E.C.T. and chlorpromazine. He received a total of 5 E.C.T.s and 75 mg. of chlorpromazine t.d.s. He responded well and left hospital on August 10.

After leaving hospital he returned to his work for about two months. He then refused to go to work or to attend the hospital. However, on September 8, 1959, he made a third attempt on his life with coal gas. This was brought about by acute worry, the patient fearing that his girl friend was pregnant by him. On readmission he was again anxious and tense, but not depressed. He was treated by sedation with phenaglate, two capsules of this preparation being given three times a day. With this treatment his condition improved until he was discharged from in-patient care on October 20. He was seen regularly as an out-patient until March 12, 1960, when he claimed that he had weaned himself off the capsules and that he felt there was no further need to attend the hospital. Objectively he was well and was quite free from symptoms.

Six weeks later, without warning he committed suicide, using about 120 hoarded phenaglate capsules for the purpose.

Post-mortem Findings.—Necropsy revealed no anatomical abnormality to account for the patient's death. Chemical analysis of the body organs and contents was carried out at the Area Home Office Forensic Science Laboratories. The following total amounts of barbiturate were discovered:

Stomach contents ..	2.7 g. (approximately 40 gr.)
Blood	3 mg./100 g.
Liver	7.5 mg./100 g.
Brain	4.1 mg./100 g.
Kidney	4.6 mg./100 g.

Analysis of the blood and liver revealed the presence of approximately equal quantities of phenobarbitone and quinalbarbitone in those tissues. Apart from the stomach contents, bemegride was found in the highest concentration in the brain. In the latter organ there was 0.7 mg./100 g. bemegride present.

These findings, together with the clinical evidence, were taken to indicate that the cause of death was barbiturate poisoning from an overdose of phenaglate capsules.

COMMENT

In view of the rapidly rising toll of deaths from barbiturate poisoning it is reasonable to attempt new steps to limit the dangerous potentialities of these widely used drugs. The best solution of all would be, of course, to stop using barbiturates altogether. Unfortunately there is as yet no alternative available that combines all the essential therapeutic properties of the barbiturates with a complete absence of toxicity. Statutory control of the prescription and issue of barbiturates has the effect of limiting addiction and the indiscriminate use of these dangerous drugs. But there still remains great danger to those who require large amounts of barbiturates for their effective management. There is the problem of the suicidal patient who hoards his drugs for an attempt on his own life, and also the problem of overdosage by accident.

The megimated barbiturates are based on the known properties of bemegride and its antagonism to barbiturates. They were introduced in an attempt to reduce the toll of deaths from barbiturate poisoning after clinical and other work by Professor Shaw and his colleagues in Australia on various combinations of bemegride with the barbiturates.

It is clearly too early to express dogmatic opinions on the relative "safety" of the megimated and "plain" barbiturates. The most one can say is that there is promise that the megimated barbiturates have less lethal potentiality than unmodified barbiturates but that there is probably a limit beyond which megimation cannot prevent the onset of coma which may be deep enough to cause death. Up to a certain hypothetical ceiling overdosage appears to be attended by less risk with the megimated barbiturates. However, the occurrence of one case in which death occurred after approximately one hundred capsules of phenaglate were swallowed must indicate that the advantages of megimated barbiturates have limits. How far these limits extend to provide a useful advantage over unmodified barbiturates must be related to the individual practice of the doctor prescribing them, the patient under treatment, and several other circumstances governing the effects of these sedative-hypnotic drugs.

We are indebted to Dr. T. M. Cuthbert, the physician-superintendent, St. Luke's Hospital, for his permission to publish this, and to Dr. A. S. Curry, of the Forensic Science Laboratories, North Eastern Area, for supplying us with the data relating to the post-mortem findings.

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Heffernan, D. T. (1959). Ibid., **2**, 1097.
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Reviews

HYPNOSIS AND ANAESTHESIA

Hypnosis in Anesthesiology. By Milton J. Marmer, M.D., M.Sc.Med.(Anes.). Foreword by John B. Dillon, M.D. (Pp. 150+xv; 54s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

The ability of hypnosis to produce amnesia and a pain-free state in many ways resembling anaesthesia has for long raised hopes that it would be a useful adjunct to, if not even a substitute for, orthodox anaesthesia. Anaesthetists have not so far shown much interest. Perhaps it is because the techniques of hypnosis are a little remote from ordinary medical ones, or perhaps it is because they make too great a demand on the emotions and confidence of the practitioner. The phenomena of hypnosis, even if imperfectly understood and somewhat unpredictable in their nature, are not in doubt, but their utilization in the field of anaesthesia has languished through lack of adequate instruction.

Sporadic lectures or somewhat theatrical demonstrations are not enough for the seriously interested anaesthetist. Lucid and devoted exposition born of long experience is necessary, and this, Dr. Marmer, himself an anaesthetist, supplies in good measure. He disabuses the reader of any idea he may have that hypnosis is a substitute for anaesthesia. Apart from special circumstances it can never be that, because of its lack of universal application and success, and because of the difficulties of imposing on the hypnotic state the various disturbances of normal physiological processes necessary for the performance of, say, thoracic surgery and neurosurgery.

Hypnosis can, however, do many other things for the patient. It can allay the anxiety of anticipated surgery, make induction of anaesthesia smoother, prevent memory of unpleasant events, reduce the doses of anaesthetic drugs, alleviate pain post-operatively, and in general change the patient's whole subjective attitude and response to anaesthesia and operation. Most anaesthetists already practise hypnotherapy of a sort without knowing it. Whether they do or not, they are bound to find absorbing interest in Dr. Marmer's book. If only they will take the first step of reading it, sooner or later they will meet the occasion when some of its advice can be put into practice, to the improvement of their anaesthetic methods and results and to the benefit of the patients.

W. W. MUSHIN.

SHERRINGTON'S CONTRIBUTION

The Discovery of Reflexes. By E. G. T. Liddell, D.M., F.R.S. (Pp. 174+vi; illustrated. 30s.) London: Oxford University Press. 1960.

Charles Sherrington repeatedly expressed the hope that no one would write his biography. His distinguished pupil and colleague has respected this wish, but in writing a short history of neurophysiology up to the year 1906, Professor Liddell has shown with a sure hand the outstanding contributions made by Sherrington to present-day knowledge. In Sherrington's early days knowledge of the nervous system was fragmentary and it was still not realized that all nerve fibres belong to nerve cells, but "he was a man who knew how to ask the right question and who knew when he had got the right answer." He gave "new impetus and unprecedented guidance in the study of reflexes and so ended the stagnation which had overtaken the uncoordinated, piecemeal efforts of the preceding half-century." This brilliant story will be read by all who study the central nervous system.

W. RITCHIE RUSSELL.

NOT-SO-MINOR SURGERY

Christopher's Minor Surgery. Edited by Alton Ochsner, M.D., F.A.C.S., and Michael E. DeBakey, M.D., F.A.C.S. Eighth edition. (Pp. 539+xv; illustrated. 73s. 6d.) Philadelphia and London: W. B. Saunders Company. 1959.

Christopher's Minor Surgery has for thirty years been well known and well used, and, judging by the distinguished names of the editors and contributors, this eighth edition is likely to prove as popular as its predecessors. We agree, however, with the editors that the title is not altogether appropriate, for there are two excellent sections—on arterial diseases and on the differential diagnosis of tumours of the neck—which would equally well grace the pages of a textbook of general surgery. The editors explain that their purpose has been "to consider those conditions that can be and should be diagnosed and treated in a physician's office, in an outpatient department of a hospital, or in a patient's house." Unfortunately the facilities available in these three places are not the same, and we gained the impression that diagnosis in the patient's home had not always been in the minds of some of the writers. The danger of diagnosing an impacted fracture as a simple sprain, and the ease with which a serious intra-abdominal injury may at times be overlooked, are not emphasized. Moreover, unless the editors consider that every patient with acute abdominal pain should be admitted to hospital, would not the insertion of a short section on the differential diagnosis of severe abdominal pain be justified? These suggestions are not made in any carping spirit, but so that an excellent book may prove even more useful.

ZACHARY COPE.

NATURAL SELECTION IN MAN

Natural Selection in Human Populations. Symposia of the Society for the Study of Human Biology. Volume II. Edited by D. F. Roberts and G. A. Harrison. (Pp. 76+viii. 20s.) New York, London, Oxford, Paris: Symposium Publications Division, Pergamon Press. 1959.

The second symposium of the Society for the Study of Human Biology took place in the centenary year of the publication of the Darwin-Wallace paper outlining the theory of evolution by natural selection, and so the symposium was given the title of "Natural Selection in Human Populations." The medical practitioner is, in a sense, at the receiving end of the effects of natural selection on mankind, and so it is important that he should understand something of the way natural selection acts. At the moment, while most is known of the action of natural selection on the frequency of single genes, the same principles may be presumed to apply to the more difficult, but medically more interesting, multi-factorial systems which control the variability of quantitative traits.

L. S. Penrose stresses the importance, as a means by which selection can maintain genetic equilibrium, of heterozygote advantage—that is, a situation in which those with one of each of a pair of allelic genes are fitter than those homozygous for either of these genes. A. R. G. Owen discusses the more complicated requirements for equilibrium where more than two allelic genes are involved, as is the case, for example, with

the genes responsible for the A B and O red cell antigens. P. M. Sheppard discusses some individual human examples of selection, the remarkable interaction of ABO and rhesus incompatibility, and the association of the ABO and secretor genes for some gastro-intestinal disorders. He considers that none of the findings hitherto are adequate to account for the apparently stable polymorphism of the genes for the ABO antigens. C. A. Clarke discusses the methods that are available to estimate the fitness of individual dominant mutant genes which cause human disorders, such as those responsible for achondroplasia and peroneal muscular atrophy. Theodore Dobzhansky discusses some of the mechanisms maintaining equilibrium in natural populations of fruit flies, and makes a point that in wild populations natural selection often acts on organized gene systems rather than individual genes. Finally, E. H. Ashton discusses the rate of change that actually appears to have occurred in the evolution of primates, so far as it can be estimated, by the scanty skeletal remains that have been discovered so far.

Many medical practitioners who are not in the habit of thinking in terms of evolutionary biology will find this book hard going but rewarding if they will persevere with it. It is evolutionary thinking which, in time, will explain the origin and prevalence of many common disorders, and sometimes even indicate the best line of treatment.

C. O. Carter.

RETINAL PHYSIOLOGY

Physiology of the Retina and the Visual Pathway. By G. S. Brindley, M.A., M.D. (Pp. 298+xi; illustrated. 35s.) London: Edward Arnold (Publishers) Ltd. 1960.

Until fairly recently the physiology of the eye consisted largely of an analysis of visual sensations. This quasi-psychological literature sometimes departed rather drastically from physiological thought on other bodily activities. Boll's classical work on visual purple in 1876 has only in recent years been translated into biochemical terms, opening an important and growing chapter on the biochemistry of vision and of the retina, whilst the fairly recent development of electro-retinography has brought studies on the retina within normal laboratory procedures. Particularly elegant experiments on primitive visual cells of invertebrates have again added considerably to our knowledge of basic processes. All these developments are very largely developments in the physiology of the retina at a time when studies on the physiology of the eye as a whole have come to deal with such specific ocular problems as the nutrition of the eye and the maintenance of ocular tension.

The literature on the retina itself has now become so immense that even the expert tends to get lost in its ramifications, and Dr. Brindley has performed a useful service in summarizing adequately and critically those aspects of retinal physiology that have a direct bearing on human vision. Three of his seven chapters are devoted to objective phenomena, while four chapters are given to a particularly thorough and critical analysis of visual sensations. This is no rehash of speculative suggestions, but an assessment of valid findings collected under stringent conditions. This monograph should do much both in defining current knowledge and in clearly indicating further lines of development. A bibliography of 40 pages is a measure of the thoroughness of this survey.

Arnold Sorsby.

SANCTITY AND PSYCHIATRY

Heroic Sanctity and Insanity. An Introduction to the Spiritual Life and Mental Hygiene. By Thomas Verner Moore, Carthusian. (Pp. 243+x. $5.) New York and London: Grune and Stratton. 1959.

The author of this book is a medical man who is also a Carthusian monk, and has practised and taught psychiatry in an American Catholic University. In it he tries to produce an acceptable compromise between some aspects of Catholic dogma and practice and some of the beliefs and practices of modern psychiatry. He has obviously set himself a most difficult task. For behaviour patterns which many psychiatrists would consider to be biological and the result of normal or abnormal brain function are often attributed to the "direct action of the Holy Spirit on the mind of man." And his psychiatric approach has always to be fitted into this sort of framework.

The book discusses those special kinds of human behaviour which can be labelled as "heroic sanctity," and may later qualify a person for canonization as a saint; and quite a large part of it is occupied with a discussion of the life of Saint Thérèse of Lisieux as a good recent example of the achievement of heroic sanctity and later canonization by the Church. Father Robo, another Catholic theologian, who has dared to label Saint Thérèse as a neuropath who had a mental breakdown, comes in for very harsh criticism indeed. Father Moore insists that by the term "neuropath" Dr. Robo can only mean that Saint Thérèse was a constitutional psychopath, and to "call a canonised saint a psychopath is therefore to call in question the judgment of the Church in her decree of canonisation." Much of the book is unfortunately written in this sort of vein.

There is, however, a fascinating discussion as to how much mental disorder is compatible with later canonization by the Church. It seems that a certain amount of anxiety or depression, either reactive or endogenous, is allowed, but any evidence of conduct based on delusional ideas is an absolute bar. And, of course, the book contains a strong attack on psychoanalysis because it holds that most religious beliefs are merely the insane delusions of the human mind.

This book shows the difficulty that psychiatry has when it is required to work within the framework of too strong an authoritarian theological system. Great strains get put on both parties. Yet both religious and psychiatric disciplines of mental healing have much to learn one from the other, if only the actual techniques used can be studied and compared and the rigid dogmas which so often lie behind them can be temporarily ignored.

William Sargant.

PSYCHOANALYTIC SOURCE BOOK

Readings in Psychoanalytic Psychology. Edited by Morton Levitt, Ph.D. With 24 contributing authors. (Pp. 413+xiv. $8.50.) New York: Appleton-Century-Crofts, Inc. 1959.

The purpose of this book is to provide source material for students of behavioural sciences. Fourteen of the 26 chapters are original contributions, the others are excerpts from previous publications. All except two of the contributors are working in the United States; most of them are attached to university departments of psychiatry. The editor, who is professor of psychiatry at Detroit, has wisely refrained from presenting the various schools of thought within psychoanalysis, and has invited contributions only from writers whose orientation has remained fundamentally Freudian.

Several of them were closely associated with Freud. It is interesting to see from this book how many of his ideas have been amplified and modified since they were first advanced. Some of these changes are no doubt due to the fact that, at least in the United States, psychoanalysis has ceased to lead an extra-mural existence so far as the universities are concerned.

Each article has been introduced by the editor with a critical preface. The contributions are of a high standard, which is only to be expected of authors such as Helene Deutsch, Frenkel-Brunswik, Greenacre, and Hartmann. Edward Glover's article on a psychoanalytic approach to the classification of mental disorders is one of the most original contributions to this thorny problem. Hoffer examines the role of defensive mechanisms in psychoanalytic treatment and warns against their indiscriminate interpretation as pathological reactions. The meaning of psychoanalytic concepts and the confirmation of theories is discussed by Frenkel-Brunswik from the point of view of an academical psychologist. There is a trenchant essay by Szasz on the relationship between psychoanalysis and present-day scientific medicine, with special consideration of psychosomatic research. Among the other subjects discussed are psychosexual development, ego and super-ego organization, normal and abnormal personality development. There is an interesting report of the treatment of an impostor by Helene Deutsch. Altogether, the editor has succeeded in his purpose of presenting an informative source book on psychoanalytic research into important aspects of human behaviour.

E. STENGEL.

Midwifery: a Textbook for Pupil Midwives is an unpretentious account at a reasonable price of what the pupil midwife needs to know to cover the Part I and II examinations of the Central Midwives Board. The authors, Gordon W. Garland and Rosemary C. Perkes, recognize that midwives deal mostly with the normal, and that if a discussion of abnormalities is wanted it can more appropriately be found elsewhere. The line drawings are clear and helpful, so it is unfortunate that the photographic plates are reproduced in such a way that they appear to have been taken in a thick fog. (English Universities Press; 290 + x pp.; 67 illustrations; index. Price 21s.)

Burns from electric currents have become commoner in recent years owing to the much more general supply of electricity and to the relatively low prices at which many domestic electrical appliances can be bought. A considerable proportion of the injuries result from attempts by the householder himself to correct defects in the wiring of his house or the appliances attached to it, and it is to help these people understand what they are doing that Mr. F. C. Searle, an electrical engineer, has written *The Householder's Electrical Guide* (Stanley Paul; pp. 127; 10s. 6d.). It is well illustrated and discusses all the ordinary problems that might arise. The author also gives some useful advice on the quality of materials (in particular flex) that should be used.

Basic Physics in Radiology, by L. A. W. Kemp and R. Oliver, is a textbook which explains simply and clearly the basic physical principles on which medical radiology depends; it is intended to help student radiographers and those studying for radiological diplomas. The authors deny that it is a "cram" book, but help the student by including questions from past examination papers and by printing the less essential information in small type. (Blackwell Scientific Publications, Oxford, 1959; 329+xiii pp.; 143 figs.; index; price £1 15s.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Vom Reichsgesundheitsrat zum Bundesgesundheitsrat. Ein Beitrag zur Geschichte des Deutschen Gesundheitswesens. By Dr. Kurt Glaser. (Pp. 144+iv; illustrated. DM. 12.80.) Stuttgart: Georg Thieme Verlag. 1960.

Ciba Foundation Symposium on Congenital Malformations. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Cecilia M. O'Connor, B.Sc. (Pp. 308+xii; illustrated. 45s.) London: J. and A. Churchill, Ltd. 1960.

Ciba Foundation Symposium on Cellular Aspects of Immunity. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Maeve O'Connor, B.A. (Pp. 495+xii; illustrated. 60s.) London: J. and A. Churchill, Ltd. 1960.

Miscellaneous Notes. (Seventh Series.) By F. Parkes Weber, M.D., F.R.C.P., F.S.A. (Pp. 12. 3s.) London: H. K. Lewis and Co., Ltd. 1960.

Furneaux's Human Physiology. (Nurses' edition.) New edition completely revised by William A. M. Smart, M.B., B.S. Lond., B.Sc.Lond., M.R.C.S.Eng., L.R.C.P.Lond. (Pp. 417+viii; illustrated. 13s. 6d.) London: Longmans. 1960.

Principles of Orthopaedic Surgery. By Paul C. Colonna, M.D. Revised edition. (Pp. 799+ix; illustrated. £7 10s.) London: J. and A. Churchill, Ltd. 1960.

Diseases of the Newborn. By Alexander J. Schaffer, M.D. Section on Neonatal Cardiology by Milton Markowitz, M.D. (Pp. 878+xv; illustrated. £7.) Philadelphia and London: W. B. Saunders Company. 1960.

Microbes, Men and Monarchs: A Doctor's Life in Many Lands. The Autobiography of Aldo Castellani. (Pp. 287; illustrated. 25s.) London: Victor Gollancz, Ltd. 1960.

Babies by Choice or by Chance. By Dr. Alan F. Guttmacher and Dr. Eleanor Mears. (Pp. 191. 12s. 6d.) London: Victor Gollancz, Ltd. 1960.

Lymphocytes and Mast Cells. By Margaret A. Kelsall, B.A., M.A., Ph.D., and Edward D. Crabb, B.A., M.A., Ph.D. (Pp. 399+xvi; illustrated. 64s.) London: Baillière, Tindall and Cox, Ltd. 1960.

Inhibition in the Nervous System and Gamma-Aminobutyric Acid. Proceedings of an International Symposium held in Duarte, California, May 22-24, 1959. Editorial Board: Eugene Roberts, Claude F. Baxter, A. van Harreveld, C. A. G. Wiersma, W. Ross Adey, and Keith F. Killam. (Pp. 591+xii; illustrated. £5.) Oxford, New York, London, Paris: Symposium Publications Division, Pergamon Press. 1960.

A History of the Nursing Profession. By Brian Abel-Smith. (Pp. 290+xiv; illustrated. 30s.) London, Melbourne, Toronto: Heinemann. 1960.

The Clinical Use of Aldosterone Antagonists. Compiled and edited by Frederic C. Bartter. With 23 contributors. (Pp. 211+xi; illustrated. 40s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Postmortem Homografts. By James Barrett Brown, M.D., F.A.C.S., and Minot P. Fryer, M.D., F.A.C.S. (Pp. 64+vii; illustrated. 44s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

The Mechanism of Action of Insulin. A Symposium organized by the British Insulin Manufacturers. Consulting Editor: F. G. Young, M.A., D.Sc., F.R.S. Editors for the British Insulin Manufacturers: W. A. Broom, B.Sc., F.R.I.C., and F. W. Wolff, M.D. (Pp. 320+xvi; illustrated. 32s. 6d.) Oxford: Blackwell Scientific Publications. 1960.

Transactions of the American Ophthalmological Society. 95th Annual Meeting, 1959. (Pp. 744+xviii; illustrated. £7 4s.) Toronto University Press. London: Oxford University Press. 1960.

The Early History of Surgery. By W. J. Bishop. (Pp. 192; illustrated. 18s.) London: Robert Hale, Ltd. 1960.

Doctors and Disease in Tudor Times. By W. S. C. Copeman, F.R.C.P. (Pp. 186+xiv; illustrated. 42s.) London: Dawson's of Pall Mall. 1960.

Clinical Applications of Diagnostic and Therapeutic Nerve Blocks. By John J. Bonica, M.D. (Pp. 354+xix; illustrated. 70s.) Oxford: Blackwell Scientific Publications. 1960.

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HOMOTRANSPLANTATION OF THE KIDNEY AFTER WHOLE-BODY IRRADIATION

Two statements about the surgical replacement of the kidney would be agreed to by all who have studied the matter. The first is that the kidney is a transplantable organ. Notwithstanding the deprivation of its nerve supply and lymphatic drainage, a kidney that has been removed and replaced or that has been transplanted elsewhere in the same body will resume its function. The second is that, for immunological reasons, true homografts of the kidney may be expected to fail.

The truth of the first proposition is attested to by a wealth of experimental work on animals[1] and by the successful transplantation of kidneys between identical twins.[2–4] As to the second, experimental and clinical experience combine to show that kidney homografts, like skin homografts, provoke an immunological reaction and succumb to it in a matter of weeks, rarely of months. "At the present state of our knowledge," said a report from the Peter Bent Brigham Hospital in 1955, "renal homotransplants do not appear to be justified in the treatment of human disease." It is very appropriate that from this same source there should now come evidence that the obstacles to the use of kidney homografts need not always be insurmountable. J. P. Merrill and his colleagues[5] describe the functional survival of a kidney homograft for more than a year. A 24-year-old man, one of twins, with a history of renal disease since the age of 7, was admitted to the Brigham Hospital with progressive uraemia. Shortly before admission he had been treated elsewhere with an artificial kidney and had received transfusions of blood; and full-thickness skin grafts had been exchanged between him and his twin brother to find out whether or not they were monozygotic.

A first blood grouping revealed that the twins shared all but one of 25 erythrocyte antigens; on later analysis all 25 were found to correspond exactly, the original discrepancy being attributed to a surviving residue of transfused cells. In spite of this correspondence, the twins could not have been identical: the skin homograft from the patient to his healthy twin was rejected, though after a decidedly longer time (about three weeks) than is usual. But the genetical correspondence between the twins was thought close enough to justify an attempt at renal homotransplantation abetted by the use of whole-body irradiation to depress the primary immune response. Accordingly a first dose of 250 r whole-body irradiation was given eight days before grafting and a second dose of 200 r one day before grafting; the transplantation itself was followed by a prompt return of renal function.

In the following week the patient became critically ill; the peripheral leucocyte count dropped below 50 per c.mm. and *E. coli* was cultured from the blood. At a second surgical operation both the patient's own kidneys were removed and found to be grossly diseased, and from about a week thereafter his condition slowly improved. The patient's own skin homograft from his twin seems to have survived about eight months, and a renal biopsy at this stage had the appearance of a homograft in the early stages of rejection. Prednisone 60 mg./day was thereupon administered for about a month, and during the course of this treatment the patient received four further doses at weekly intervals of 50 r whole-body irradiation. Thereafter, so far as the present report goes, the patient remained free of symptoms and resumed his studies at college.

Two other reports, both from Paris, tell essentially the same story. In the more recent report, R. Küss and his colleagues[6] describe the admission of a 41-year-old man on the recurrence of a kidney disease for which his left kidney had been removed four years before. According to a strategy carefully worked out beforehand and kept to strictly, the right kidney (now almost wholly occupied by an epithelioma) was removed; haemodialysis on the fourth day and a single whole-body dose of 400 rads from a cobalt source on the fifth day was followed, on the sixth day, by the transplantation of a kidney from his 47-year-old sister. (The donor had been treated for three days beforehand with cortisone and 6-mercaptopurine with the idea of diminishing any complications that might arise from a "graft against host" reaction.[7]) An anuric crisis two days after its transplantation called for the decapsulation of the graft,

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[3] Ginn, H. E., jun., Unger, A. M., Hume, D. M., and Schilling, J. A., *J. Lab. clin. Med.*, 1960, **56**, 1.
[4] Dossetor, J. B., MacKinnon, K. J., Luke, J. C., Morgan, R. O., and Beck, J. C., *Lancet*, 1960, **2**, 572.
[5] Merrill, J. P., Murray, J. E., Harrison, J. H., Friedman, E. A., Dealy, J. B., and Dammin, G. J., *New Engl. J. Med.*, 1960, **262**, 1251.
[6] Küss, R., *et al.*, *Presse méd.*, 1960, **68**, 755.
[7] See *Brit. med. J.*, 1958, **2**, 1341.
[8] Hamburger, J., *et al.*, *Presse méd.*, 1959, **67**, 1771.
[9] Dammin, G. J., Couch, N. P., and Murray, J. E., *Ann. N.Y. Acad. Sci.*, 1957, **64**, 967.
[10] Calne, R. Y., *Lancet*, 1960, **1**, 417.

which was exposed to a further local dose of 150 rad. Apart from the expected sequelae of the irradiation itself, which required the transfusion of 14 litres of blood over a period of about two months, the patient's condition improved steadily, and he returned home three months after the transplantation. Kidney function was adequate but by no means normal; its inadequacy may or may not have been due to immunological causes.

An earlier case described by J. Hamburger and colleagues[8] has one feature of special interest. A 37-year-old male victim of long-standing renal disease, probably glomerulonephritis, received a total of 460 rad whole-body irradiation in two doses six days apart in preparation for the grafting of a kidney from his non-identical twin brother a day later. The transplanted kidney resumed function and worked well for some 15 days; then, at just about the time a homograft reaction would be expected, an anuric crisis supervened and the blood urea rose four-fold. Happily an improvement began on the 22nd day, and has been maintained for the period which the report describes; after four months renal function was judged about 80% normal.

In both the cases reported from Paris, donor and recipient enjoyed a close correspondence of red-cell and leucocytic antigens. In the one case the donor possessed only one red-cell antigen (C) that was not also present in the recipient, and the leucocytic antigens were qualitatively indistinguishable. In the second case likewise no leucocytic antigen and only one red-cell antigen (Le^a) recorded in the donor was absent in the recipient, and it is noteworthy that a skin graft transplanted from the kidney's recipient to its donor survived for as long as 25 days.

These bald accounts do not do justice to the wealth of medical care lavished on these patients and the scrupulous attention to detail at all stages; neither the decision to transplant a kidney nor its execution were lightly undertaken, and the execution itself called upon a very wide range of technical resources. It is hardly yet possible to interpret the results. In all three cases there was evidence that a homograft reaction, however feeble, was actually in progress, and it is therefore a reasonable presumption that a transplanted kidney can put up with some immunological opposition without ceasing to work. But immunological crises may recur and will undoubtedly be looked for. As to the factors that reduced the immunological reaction to a level supportable by the graft, all three groups of authors are agreed that the specially close genetical relationship between donor and recipient, the history of chronic uraemia in the recipient,[9] and the irradiation must each have played some part; and to these may be added the episodes of treatment with corticoids and (for whatever they may signify) the repeated transfusions of blood. The purely additive co-operation of these factors, with irradiation making the biggest single contribution, may well be thought to have incapacitated the immune response to a degree which made possible the functional acceptance of the graft; and here we may recall the promising preliminary results that have been secured by the treatment of dogs with 6-mercaptopurine before the transplantation of a kidney.[10] The Boston authors[5] are inclined to think in terms of a state of induced tolerance—that is, to interpret the long survival of their kidney homograft in terms, not of a primary immunological incapacity, but of an active specific suppression of the immune response associated with exposure to antigen over a period during which the immunological response system was enfeebled. However that may be, the outcome is that three people who would otherwise probably have died were given an extra lease of reasonably normal life, and by methods which can be reproduced exactly when equally favourable opportunities present themselves.

ASCITES IN LIVER DISEASE

One of the most difficult problems in liver disease is the management of the patient with ascites. The accumulation of fluid in the peritoneal cavity in portal cirrhosis implies that the functioning of the liver cells is seriously impaired, for, in the absence of complicating factors such as thrombosis of the portal or hepatic veins, it originates in the combination of portal hypertension and a reduced colloid osmotic pressure. The latter is a reflection of the lowered concentration of serum albumin due to failure of protein synthesis by the damaged liver. Precise correlation of these two factors with formation of ascites has not been established, though it is

[1] Post, J., and Patek, A. J., Jr., *Arch. intern. Med.*, 1942, **69**, 67.
[2] Luetscher, J. A., and Johnson, B. B., *J. clin. Invest.*, 1954, **33**, 1441.
[3] Preedy, J. R. K., and Aitken, E. H., ibid., 1956, **35**, 430.
[4] Ralli, E. P., Robson, J. S., Clarke, D., and Hoagland, C. L., ibid., 1945, **24**, 316.
[5] Browne, J., *Phil. Trans. B.*, 1685, **15**, 1266.
[6] Madden, J. L., Loré, J. M., Jr., Gerold, F. P., and Ravid, J. M., *Surg. Gynec. Obstet.*, 1954, **98**, 385.
[7] Neumann, C. G., Adie, G. C., and Hinton, J. W., *Ann. Surg.*, 1957, **146**, 700.
[8] Herringham, W. P., and Hadfield, C. F., *St Bart's Hosp. Rep.*, 1905, **41**, 25.
[9] Eisenmenger, W. J., *Ann. intern. Med.*, 1952, **37**, 261.
[10] Atkinson, M., Paton, A., and Sherlock, S., *Lancet*, 1954, **1**, 128.
[11] Read, A. E., Laidlaw, J., Haslam, R. M., and Sherlock, S., *Brit. med. J.*, 1958, **1**, 963.
[12] Marson, F. G. W., *Lancet*, 1954, **2**, 847.
[13] Giuseffi, J., Werk, E. E., Larson, P. U., Shiff, L., and Elliot, D. W., *New Engl. J. Med.*, 1957, **257**, 796.
[14] Radó, J. P., Blumenfeld, G., and Hammer, S., *Amer. J. med. Sci.*, 1959, **238**, 542.
[15] Kerr, D. N. S., Read, A. E., Haslam, R. S., and Sherlock, S., *Lancet*, 1958, **2**, 1084.
[16] *Brit. med. J.*, 1960, **2**, 364.
[17] Shaldon, S., McLaren, J. R., and Sherlock, S., ibid., 1960, **1**, 609.
[18] Freedman, P., Moulton, R., and Spencer, A. G., *Clin. Sci.*, 1958, **17**, 247.
[19] Dingman, J. F., and Yoffee, H. F., *New Engl. J. Med.*, 1960, **262**, 585.

generally held that levels of serum albumin below 3.1 g. per 100 ml. are critical.[1] When fluid begins to accumulate, other mechanisms tend to perpetuate retention of salt and water. The most influential of these is probably the salt-retaining hormone of the adrenal cortex, aldosterone, increased amounts of which have been found in the urine of these patients,[2] though oestrogens[3] and to a less extent antidiuretic hormone of the posterior pituitary[4] may play a part. Their effects could be due either to overproduction or to failure of destruction by the damaged liver, but in any case are probably secondary.

Fifteen years ago almost the only treatment for ascites was by paracentesis abdominis. This had two serious drawbacks; the removal of large quantities of fluid and electrolytes in equilibrium with the extracellular fluid could lead to collapse and even death[5]; and the removal of large quantities of protein results in serious depletion of body stores, which cannot be replaced by hepatic synthesis. Surgical operations[6 7] to increase the absorptive area of the peritoneal cavity have their advocates, as does porta-caval anastomosis. But it cannot be stressed too strongly that patients with cirrhosis and ascites are poor operative risks, and the burden of treatment must fall on the physician. The recognition of the part played by salt retention has been an important advance, although the value of salt deprivation was appreciated many years ago.[8] Bed-rest, a "salt-free" diet, and organic mercurials, supplemented if necessary by ammonium chloride, will produce a satisfactory diuresis in many patients with ascites, provided they are willing to submit to treatment which may last many weeks.[9 10] Formation of ascitic fluid is halted and the level of serum albumin tends to rise. The judicious use of a high-protein diet, together with salt-free protein supplements, may further aid recovery, while infusions of salt-poor human albumin should be reserved for the occasional patient, because of the transitory nature of their effect on the plasma proteins. Ion-exchange resins have proved disappointing in controlling ascites, and oral thiazide diuretics should be given with great care because of the risk of precipitating hepatic failure.[11]

Fresh hope for the patient with intractable ascites has come from attempts to inhibit adrenal cortical overactivity. Bilateral adrenalectomy has been tried,[12 13] but the results are hardly impressive enough to justify such a radical approach. There is no doubt that in some cases synthetic steroids will promote a diuresis, especially if combined with thiazide derivatives, and there is a recent encouraging report on the use of methyl prednisone in this way.[14] It is possible that steroids act by inhibiting production of aldosterone. Amphenone, which is a direct adrenal inhibitor, is too toxic for routine use in man, but the spironolactones are more promising.[15 16] These substances appear to compete with aldosterone at its peripheral site of action on the distal renal tubule, thus causing a salt-and-water diuresis. They have little effect on potassium excretion, an advantage in patients with cirrhosis, and can be used in conjunction with diuretics, which act on the proximal tubule. The compound at present available can be given by mouth in doses of 100 mg. or more four times a day, and is free from serious toxic effects. Its action, however, is delayed for several days, and it is probably unwise to continue treatment for longer than a week or ten days at a time. If effective it appears to break the vicious circle of salt retention and secondary aldosteronism, thus enabling the disorder to be controlled on conventional treatment. The beneficial effect of spironolactones and diuretics can be further enhanced by the intravenous infusion of mannitol in order to promote a water diuresis.[17] Somewhat similar is the recent observation[18 19] that calcium gluconate will enhance excretion of sodium in patients with oedema, though here the mechanism may be due to competition between calcium and sodium for reabsorption by the renal tubule.

The availability of several means of treating ascites has certain disadvantages. The disturbance of electrolyte and water metabolism in this condition is a complex one, and therapy may lead to dangerous situations such as hypokalaemia, hyponatraemia, and hepatic failure. Proper understanding of the rationale of treatment and facilities for biochemical and other means of control are essential.

CRISIS IN ELECTROENCEPHALOGRAPHY

Electroencephalographic departments are worried by their difficulties in finding and in keeping E.E.G. recordists, and by the consequent loss of standards, technical and scientific, which a survey of units throughout the country has disclosed. The E.E.G. is now an integral part of the investigation of nervous and mental disease, but there are not many clinicians who can give enough time to train in this corner of neurophysiology so as to make themselves entirely competent, or who can sustain enough interest in it to foster an inquiring, stimulating atmosphere in the departments they lead. A committee[1] of the Royal College of Physicians reported two years ago that, "In the past decade about a hundred new departments have been established in the British Isles, but there has been no commensurate increase in knowledge, in scientific

[1] See annotation, *Brit. med. J.*, 1958, 1, 389.

inquiry within the departments or critical application of the techniques available, in contrast to some other countries."

Standards of recording have been laid down by the International Federation of Societies of Electroencephalography, but the practice of scores of departments falls lamentably below them, and in this regard Britain, which pioneered in the field, is now a long way behind. The main reason for this is that doctors do not really want to become clinical electrophysiologists, though they do not mind having control of a department, for interest, convenience, or prestige. Senior registrars in neurology or psychiatry may take a course of instruction, and at interview by appointment committees they are able to profess knowledge of electroencephalography and so enhance their chances of appointment to a clinical consultant post in a hospital where a department exists. Having been successful, they are inevitably drawn to, and engulfed by, their clinical task, and the neurophysiological laboratory languishes under an inadequately informed or absentee medical director.

A survey carried out in almost a hundred departments in the United Kingdom by the Electroencephalographic Society led to these observations:

"Many departments with a titular head of high status are in effect managed by amateur or part-time specialists or even technicians with little or no training, inadequate remuneration, and no prospects of promotion or advancement. There is a high correlation between systematic training and long experience on the one hand, and ability to use varied and specialized methods on the other. None of the centres with untrained workers uses auxiliary techniques or adapts the examination to the special needs of referring physicians or to the patient's condition. There are very few full-time workers with consultant status or teaching experience in the field. Nearly half of the departments surveyed have had to reduce their scope because of lack of skilled staff and some have come to a complete standstill."

In the view of the council of the E.E.G. Society there is a vicious interaction between two faults—the lack of systematic instruction by experienced teachers and of reasonably paid posts for those trained.

The other side of the picture is of rapid increase in knowledge and the use of new techniques in electrophysiology which call for informed pupils and enthusiastic technicians. E.E.G. departments must be prepared to record from the depth of the brain in a neurosurgical operation, from muscles, from the heart, and from the viscera: they may have to aid the anaesthetist and thoracic surgeon as well as the neurologist and his colleagues, and they have to use pharmacological and physical techniques of increasing complexity.

The inevitable conclusion is that if the present unhappy state of affairs is to be corrected there must be a major change in the recruitment, training, and terms of service in this specialized field in order to attract doctors and technicians with a sense of vocation. The Royal College of Physicians advised on all this two years ago, urging more whole-time and maximum part-time consultant appointments, but little has been done.

A NEW TETRACYCLINE

In 1957 J. R. D. McCormick and his colleagues[1] isolated a new tetracycline antibiotic which was produced by a mutant of Duggan's strain of *Streptomyces aureofaciens*. This is now known as demethylchlortetracycline (D.M.C.T.), and there have been a number of preliminary reports in the American literature of its pharmacological and therapeutic effectiveness. These have been reviewed in the opening pages of this issue by Dr. Maxwell Finland and Professor L. P. Garrod, who also include further interesting observations of their own. It seems reasonably certain that this is a useful addition to the tetracycline group of antibiotics. It is more stable than the others, requires lower and less frequent doses, and attains more effective and prolonged antibacterial concentrations in the blood. The basic research of C. M. Kunin, A. C. Dornbush, and M. Finland[2] into the distribution and elimination of four tetracycline analogues in normal men has shown that D.M.C.T. has a slow renal excretion and the longest "half-life" of the four. The studies of W. P. Boger and J. J. Gavin[3] have shown that small quantities of D.M.C.T. penetrate into the cerebrospinal fluid through uninflamed meninges after a single oral dose of 500 or 1,000 mg. It is quickly absorbed from the gastrointestinal tract in most subjects, though this is not invariable.

The antibacterial range of activity of D.M.C.T. is generally similar to that of the other tetracyclines. As might be expected, cross resistance is complete whether this has been induced in the laboratory or demonstrated *de novo* as a natural phenomenon. The *in vitro* activity of D.M.C.T. has been very fully investigated against many strains of human pathogens. It appears to be more active than tetracycline against most organisms, or at least of equal activity and very rarely less. Finland and Garrod comment fully on the merits of this new antibiotic and give a fair assessment of its place in therapeutics in comparison with the older and more familiar tetracyclines. They confidently conclude that only two daily doses of D.M.C.T. are required—a great advantage, especially in treating out-patients—and that a smaller dose of D.M.C.T. than of tetracycline should achieve an equivalent therapeutic result. In their opinion D.M.C.T. may well prove to be the preferred tetracycline of the future provided no unforeseen drawbacks to its apparent advantages are discovered. A phototoxic reaction is a rare side-effect of this antibiotic, but in Britain this is not likely to be troublesome. Diarrhoea may occur in over 30% of patients receiving high doses of D.M.C.T. The problem of tetracycline diarrhoea is a thorny one and argument about its cause continues. Whether the inclusion of a chlorine atom in the chemical structure of this antibiotic will lead after prolonged usage—as, for example, in the treatment of chronic bronchitis—to liver damage or even to bone-marrow dysfunction remains to be seen. So far there have been no reports of such toxicity, but with any new

[1] McCormick, J. R. D., *et al.*, *J. Amer. chem. Soc.*, 1957, **79**, 4561.
[2] Kunin, C. M., Dornbush, A. C., and Finland, M., *J. clin. Invest.*, 1959, **38**, 1950.
[3] Boger, W. P., and Gavin, J. J., *Antibiotics Annual, 1959-1960*, p. 393.

and potentially toxic drug several years may elapse before toxic effects of this kind are reported. Finland and Garrod do not suggest that the relative merits of D.M.C.T. can yet be finally assessed: it is a promising newcomer with several well-ascertained advantages, but it has yet to gain its spurs in the everyday treatment of infective disease.

RUBELLA AND CONGENITAL DEFECTS

Ever since N. M. Gregg[1] first pointed out the connexion between rubella in a pregnant woman and congenital defects in her baby, an important problem has been to estimate the size of the risk. A helpful contribution to this has now appeared from the Ministry of Health and the General Register Office.[2] It is a report on an inquiry carried out with the help of all medical officers of local health authorities in England, Scotland, and Wales during 1950–7. All who took part in this investigation deserve congratulations, for their work has helped to answer some questions of outstanding importance. In a preface to the report Sir John Charles emphasizes two conclusions: first, the risk that rubella in early pregnancy will cause malformation in the infant is much less than originally suggested; secondly, deafness should be specially looked for in these cases.

In contrast to most previous inquiries, which began from the affected child, this inquiry began from the mother. Consequently a much better estimate of the risk is obtainable. In all, 578 cases of rubella in pregnancy were recorded, of which 202 were of infection in the first 12 weeks; all had been selected before the birth of the child. Control cases numbered 5,717. The first main conclusion is that rubella after the 16th week of pregnancy did not affect the foetus. Secondly, when the mother had had rubella within the first 12 weeks of pregnancy the risk of death for the baby in utero or up to 2 years of age was about double the risk for babies in the control series. The following figures from the report are relevant: in cases of rubella up to 12th week of pregnancy 5.0% resulted in abortion compared with 2.4% of the controls; 4.5% resulted in stillbirth compared with 2.4%; and 6.9% died under the age of 2 years compared with 2.4%. But in addition the babies in the rubella series who survived to 2 years old included a considerable proportion with congenital defects. The actual percentages for the rubella series, with those for the control series in parentheses, were: congenital heart disease 4.7 (0.2), cataract 4.7 (0.04), deafness 3.0 (0.08), suspected deafness 3.6 (0.4). In addition mental defect affected 1.8% of the rubella series against 0.4% of the controls and pyloric stenosis 1.2% against 0.2%. There were also other small differences. Later examination of the children at 3–5 years old showed that the incidence of impaired hearing after maternal rubella in the first 12 weeks of pregnancy is about 19%, but in only a small proportion was it a severe handicap.

As to other virus diseases, measles was found to be followed by a somewhat higher incidence of infant deaths and malformations, but "the numbers are too small and the defects too varied to suggest an association with the maternal measles infection." Chicken-pox and mumps appeared to have no harmful effect on the child. Influenza did not certainly do so, though an unusually high death rate was noted among infants under 2 years. Poliomyelitis is well known for its serious effects in the pregnant woman: of the six cases in which it occurred in this series, the children survived to 2 years in only two.

PROPERTIES OF CATGUT

What qualities does the surgeon expect to find in catgut? Not only is strength required, but strength which will endure until the wound is firmly healed. Then the sooner the suture material is gone the better, because it may give rise to annoying sepsis if it persists in a wound.

Catgut is made from the submucosa of lamb's small gut. Intestinal submucosa contains little else besides blood vessels, and therefore catgut is virtually a yarn spun from blood-vessel filaments; it consists chiefly of collagen and elastic fibres. As a foreign protein it would be expected to cause an allergic response, but this is fortunately rare. It is destroyed in the body in two ways. Plain untreated catgut excites a pyogenic reaction; the polymorphonuclear leucocytes in the pus produce enzymes which rapidly digest the material. Tryptic ferments of the alimentary tract also digest it readily; enzymes secreted by common pyogenic organisms have a similar effect. Infected wounds or incisions contaminated by the contents of the small bowel are therefore likely to give way owing to early destruction of the catgut. The second way in which catgut is removed from tissues is by the foreign-body giant-cell reaction, which is much the slower of the two. Treatment of gut with chromic acid greatly increases its resistance to digestion and also decreases its pyogenic properties. Thus, untreated catgut after seven days in the body will be surrounded by sterile pus and half digested away, whereas chromic catgut will be virtually intact and have a minimum cellular reaction round it. P. Lawrie, G. E. Angus, and A. J. M. Reese[1] showed that size 0 chromic catgut excites chiefly a giant-cell reaction, which does not effectively diminish its strength for ten days.

In a recent paper Lawrie and Angus[2] record their measurements of the tensile strength of different types of gut after embedding them for various periods of time in hamsters. They found that, whereas all varieties of plain catgut had lost effective strength in five days, size 0 chromic gut was strong up to ten days and the thicker size 2 chromic up to twenty-one days. One interesting result of their experiments is that size 2 chromic gut excites a delayed pyogenic reaction; gut removed between 14 and 35 days is surrounded by frank

[1] Gregg, N. M., *Trans. ophthal. Soc. Aust.*, 1941, 3, 35.
[2] Manson, M. M., Logan, W. P. D., and Loy, R. M., *Rubella and Other Virus Infections during Pregnancy*. Ministry of Health, 1960. H.M.S.O. (7s.).

[1] Lawrie, P., Angus, G. E., and Reese, A. J. M., *Brit. J. Surg.*, 1959, 46, 638.
[2] —— —— ibid., 1960, 47, 551.

pus. This is not true of the finer variety of chromic gut. These authors therefore advise that the maximum thickness of chromic gut should be that of size 0 and that the thicker varieties may lead to impaired wound healing because of the development of sterile pus round the material.

Their results will certainly be a warning against using thick chromic catgut for ligatures in the peritoneal cavity, for loops of small gut may become adherent to such sterile abscesses. It is doubtful, however, whether everyone would agree with their conclusions about the general unsuitability of thick chromic gut. The sterile abscesses form only after the wound is firmly united, and in practice they are not found to give rise to subsequent trouble. It is not only the suture material which prevents dehiscence of abdominal wounds but the state of the tissues themselves. A few days after operation the fascia of the abdominal wall softens, and it is common experience when resuturing a burst abdomen to find that the sutures have cut through tissues rather than themselves snapped. The thicker catgut has the advantage that by virtue of its very dimensions it does not cut through friable tissues as does the thin variety, on the analogy of wire and cheese. Before most surgeons will be convinced that no grade of chromic catgut greater than 0 need be used in suturing the abdomen, a controlled series of cases will have to be presented in which standard laparotomy wounds are sutured with several different strengths. Clinical experience and animal experiments seem to be in conflict here, and it is important that the discrepancy be further investigated.

CONTENDING VACCINES

The approval which the United States Public Health Service recently gave to A. B. Sabin's strains of poliovirus for the production of live vaccines has evoked a protest from H. Koprowski (see p. 1013). He criticizes the "exclusive endorsement" of one set of strains, summarizes some data on the safety of his own strains of virus, and suggests that a fair scientific judgment would disagree with the U.S. Public Health Service's action. This is not only a domestic matter but is of some moment to other countries, because they could not import, for general use, a vaccine from the U.S.A. unless it were officially approved there.

Of the three vaccines undergoing extensive trials, Sabin's and Koprowski's have been given to many millions of people without ill-effect. Administration of vaccine made from H. R. Cox's strains has been followed in Florida and West Berlin by cases of paralysis, but a relationship of cause and effect has not been proved; this is still being investigated. In bestowing approval on the Sabin strains and withholding it from Koprowski's, the U.S. Public Health Service was guided by neurovirulence tests in monkeys. These tests are somewhat imprecise. They can indicate large differences in virulence to man, but their sensitivity as indicators of small differences is not yet determined. And it would seem to be on data lying in this uncertain zone that the decision rests to discriminate between the Sabin and Koprowski strains.

In feeling impelled to make a decision at all at present, the U.S. Public Health Service probably responded to the opinion held in many countries, including the U.S.A., that at least one live vaccine of tested safety and efficacy should be made generally available. If one is thus to be endorsed, the reasonable choice is Sabin's. This is the vaccine being tried out in Great Britain at present. But in this rapidly growing field it is obviously important that no decision should be taken which would impede the development and testing of alternative vaccines.

THE BEIT FELLOWSHIPS

The great benefactions, private and public, that have helped to advance medical research in the last two to three decades are so much part of the medical scene that it comes as a surprise to be reminded of how hard was the lot of the medical investigator only 50 years ago. Though a few scholarships were available, research was usually an unpaid occupation. It may have been the more individual and zealous for that, but the needs of the day were changing, and it was in admirable anticipation of them that Otto Beit founded in 1909, as a memorial to his brother Alfred, the Fellowships that bear their name. The occasion is fittingly celebrated in a small book, recently published for the trustees, recounting the first 50 years of these Fellowships and how they came to be founded.

Alfred Beit made a fortune in South African gold and diamond mines in association with Cecil Rhodes, and was in business in London when Otto came over from his native Hamburg to join him in 1888. When Alfred died in 1906 his wealth passed to Otto, who not only gave £215,000 to found the Fellowships but laboured until his death in 1930 to see that they were used well. He was created K.C.M.G. in 1920 and a baronet in 1924; in the same year he was elected F.R.S.

A close link with London University was established from the beginning and is perpetuated by the presence of the Principal on the board of trustees. Many other distinguished men have guided the destinies of this Trust, and the first advisers included Osler, Clifford Allbutt, and E. H. Starling. Of the honorary secretaries, the first was Sir James Fowler and the latest is Sir Roy Cameron. In the first fifty years 297 Fellows had been elected, numbering among them two who were to receive Nobel prizes for chemistry (Sir Alexander Todd and Dr. F. Sanger), two on whom the Order of Merit has been conferred (Professor Wilder Penfield and Sir Macfarlane Burnet), and one who has received a barony (Lord Cohen of Birkenhead). The present secretary of the Medical Research Council (Sir Harold Himsworth) and also his predecessor, the late Sir Edward Mellanby, were Fellows—Mellanby in the first year of the foundation. To-day the possessor of a Beit fellowship is receiving something more than cash, for he is keeping uncommonly good company too.

THE VALUE OF EMPHASIS IN ELIMINATING ERRORS

A CONTROLLED STUDY IN TEACHING

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Every teacher knows that in his field there are a number of errors which a proportion of students make with varying frequency year after year. The sources of these errors are not usually known, though one may suspect outdated or misleading textbooks, or defective communication between teachers and students. Examples of errors of this kind which arise in pharmacology and therapeutics are that folic acid is an effective treatment in pernicious anaemia, that atropine relaxes skeletal muscle, or that suxamethonium is a ganglion-blocking agent. Whatever the origin of such errors, it is better that they should be dispelled, and at this point two extreme approaches are possible. One is to waste no opportunity of warning students of these errors, and to draw their attention specifically to them. The other is to note the risks of putting misconceptions before a not always critical or fully receptive audience, and to aim to avoid these errors by never even hinting at their possibility.

Different teachers probably adopt intermediate practices according to their temperaments and experiences, but it is desirable and possible to obtain objective evidence on the relative merits of the two procedures by a properly designed controlled experiment. Such experiments are not original. For example, an experiment designed to find a way of eliminating typing mistakes (Holsopple and Vanouse, 1929) indicated that emphasis on the errors was more efficient than emphasis on the correct spelling. On the other hand, Peak, Brooks, and Hobson (1941) could find no difference between two groups of students making spelling mistakes when one group had received practice in the correct spelling and the other group in an incorrect version. But a proper investigation of this sort appears not to have been made in medical teaching and we have therefore studied the matter as follows. A number of misconceptions were selected and the extent to which they were held by a class of students was tested by a suitable examination. The misconceptions were then divided into two groups of equal average popularity. For the next four months each misconception in one group was deliberately discredited whenever it was relevant to mention it, while misconceptions in the other group received no special attention. At the end the prevalence of the misconceptions in each group was estimated by means of further examinations.

Method

The investigation was carried out during a course in pharmacology, which was interdigitated with other subjects over six months during the first clinical year. The 53 students concerned had already received some teaching in pharmacology in their preclinical course. They had also at this time taken part in an experiment in teaching methods (Joyce and Weatherall, 1959), and may have expected further experiments during the part of the course now being discussed. But the present experiment was not mentioned to the students until it had been completed. The students were taught by lectures, seminars—that is, meetings of not more than 15 students for discussion with a teacher—and practical work, which was mainly clinical and arranged on a project system. The course was given by four teachers, who participated equally.

Before the course began, the teachers jointly prepared a list of 24 items all of which were believed to be commonly a source of confusion, misconception, or error among students. Some of the items related to what the students had been taught in their preclinical course and the rest to what they were going to be taught. An open-ended short-answer test was prepared containing these 24 items in random order and was given to the students at the first session of the course. The questions are shown in Table I, but the order in which they were presented to the students was different and the material was not at that stage subdivided. The test required that the students should write their own answers; it did not put the possible misconceptions before them. The misconceptions were a heterogeneous collection of varying importance. Some, such as the use of folic acid in pernicious anaemia (item A 8) and the effect of underdosing with an antibiotic (B 10), were directly relevant to clinical practice. Others were mainly useful to test understanding of pharmacological mechanisms—for example, A 4, B 2. It is possible that some of the answers which are here being called misconceptions are considered acceptable by other teachers. This possibility does not affect the validity of the present experiment, which was concerned with what the students learnt from what they were taught. However, we have no reason to think that the students concerned were receiving other teaching which conflicted with the present experimental material.

The replies to the short-answer test showed that some of the expected misconceptions were in fact widespread while others appeared rarely or not at all (Table I, column 3). In the light of these replies the 24 items were paired, mainly with reference to the frequency with which they had revealed misconceptions and to some extent with regard to subject-matter, and each pair was divided at random (by tossing a coin) into an item to be emphasized and a control item. For the benefit of the teachers on the course, the 12 treated items were listed in a way which emphasized the misconception to be avoided, and the 12 control items were listed with minimal attention to possible misconceptions. A copy of this list was given to each of the four teachers and to no one else. Throughout the course the treated items were commented on by the teachers with warnings about possible errors, while the control items were mentioned with no more reference to the misconceptions than seemed essential for sound teaching. It was recognized by all the teachers that their first duty was the proper education of the students, and the restraints required by the experiment were held second in importance to this principle.

Record forms were provided to the four teachers so that the success or otherwise with which these directions

were carried out was recorded after each session. The record forms were arranged to show the time and date of the teaching sessions, the time and date of the entries about these sessions, the number of students present, and the items mentioned and how they were mentioned at the session. It was therefore possible at the end of the experiment to discover the extent to which the various items had been presented to students, and how far stress had after all been laid on misconceptions which it had been planned not to emphasize.

At the end of the course a second test was given to all the students. It consisted of three parts. The first part was identical with that given at the beginning of the course—that is, it consisted of 24 questions to which the students had to provide the answers—and this test was completed and handed in before the second was issued. The second part consisted of a further 24 questions, closely similar in substance, though not all worded exactly as before, and to each of these questions four answers were attached, from which the student had to select and mark the one which he thought most nearly correct. These answers in each case included one consistent with departmental teaching, and one, or occasionally more, popular misconceptions; the remaining answer or answers were designed to look plausible while being appreciably different from either the accepted or the selected misconceived replies. This four-way choice test, like the open-ended test, was completed and handed in before the third was issued. The third test was mainly concerned with collecting students' opinions on the course, and is not wholly relevant to the present experiment. It included certain questions, such as whether the students were aware of any experiments being conducted during the course, to which further reference is made below.

After the course and these tests, and before the professional examinations, defects in knowledge revealed by the tests were discussed with the students and further teaching was given by those methods which appeared most likely to be effective in eliminating errors.

Results

Test Scores

Forty-two students took the initial test and 52 took the final tests. One of the orginal 42 was absent on the second occasion, and the analysis which follows is based on the 41 complete sets of tests.

The frequency with which the individual specified misconceptions occurred in the open-ended tests given before and after the course and in the four-way choice test given after the course is shown in Table I. The items in the table are divided into two groups—those to which attention was specially drawn and the control items. The total frequency of misconceptions in each group for each test is shown in Table II. It will be seen that the questions were successfully chosen in that expected errors appeared in as many as 352 out of 984 possible answers. This rate is, of course, not typical of the students' performance. The matching of the two groups was reasonably satisfactory, with misconception rates of 36.6% and 35.0% respectively; close correspondence was to be expected from the method of pairing adopted.

The outcome of the experiment is seen in Table III. At the end of the course misconceptions in both groups were less frequent, but the rate decreased much more for those misconceptions which were emphasized than for those which were not. In the open-ended tests the reduction in rate in the control group does not reach conventional levels of significance ($\chi^2=2.03$, $n=1$, $0.2>P>0.1$), but the reduction in the treated group is highly significant not only when the initial rate is used as a standard but also when the results achieved in the control group are compared ($\chi^2=15.1$, $n=1$, $P<0.001$). It is clear that misconceptions became much less frequent when students were deliberately warned against them, whereas little improvement occurred when no special measures were adopted. The results with the 4-way choice test, which was administered only at the end of the course to avoid introducing the

TABLE I.—*Questions, Misconceived Answers, and Frequency of Their Occurrence Before and After the Course*

	Misconceived Answer	Frequency		
		Before Course.	After Course	
		Open	Open	4-way
Items Emphasized				
A 1. What is the action of therapeutic doses of oxytocin on smooth muscle?	Contraction (unqualified)	34	27	9
A 2. What is the effect of therapeutic doses of atropine on autonomic ganglia?	Blocks transmission	28	15	12
A 3. To what class of purgatives does castor oil belong?	Lubricant	27	4	8
A 4. How does morphine cause constipation?	Relaxing intestine	22	8	14
A 5. How serious is the danger of addiction to pethidine?	Unimportant	21	3	10
A 6. By what mechanism does digitalis slow the heart?	Slows conduction. Lengthens refractory period	13	18	27
A 7. Is adrenaline a safe agent for treatment of cardiac asthma?	Yes	12	2	5
A 8. What is the effect of folic acid in pernicious (Addisonian) anaemia?	Beneficial (unqualified)	9	5	13
A 9. What action does ethyl alcohol have on the cerebral cortex?	Stimulant	8	2	4
A 10. For what therapeutic effect is aspirin most used?	Antipyretic	5	12	12
A 11. How does mersalyl cause diuresis?	Irritates renal tubules	0	0	2
A 12. How does an overdose of adrenaline cause death?	Systolic arrest. Atrial fibrillation	1	2	0
	Total	180	98	116
Control Items				
B 1. What is the effect of therapeutic doses of suxamethonium on autonomic ganglia?	Blocks transmission	21	27	24
B 2. At what site is atropine acting when it blocks parasympathetic activity?	Ganglia. Nerve endings	31	22	31
B 3. What causes death after overdosage with chloroform?	Respiratory failure	23	12	17
B 4. How does vasopressin inhibit diuresis?	By constricting renal blood-vessels	24	19	18
B 5. What is the effect of mepyramine on gastric secretion?	Prevention	21	17	24
B 6. How does cascara sagrada purge?	Direct action	11	20	11
B 7. What is the mechanism of death in mammals after an overdose of digitalis?	Systolic arrest. Heart-block. Atrial fibrillation	12	17	27
B 8. How does noradrenaline slow the heart in man?	Direct action on pacemaker	9	5	2
B 9. What is the effect of therapeutic doses of atropine on transmission of impulses from motor nerve to voluntary muscle?	Blocks transmission	9	8	9
B 10. What effect do small repeated doses of an antibiotic have on the development of drug resistance?	Prevents resistance developing	4	0	0
B 11. What effect does physostigmine (eserine) have on cholinesterase?	Destruction	5	2	4
B 12. What causes death after overdosage with ether?	Cardiac failure	2	2	2
	Total ..	172	151	169

students to the misconceptions to a greater extent than had occurred anyway, agreed quite closely with the results of the open test. Since the students acted on the instruction in the choice test and answered all questions, by guesswork if necessary, the slightly

TABLE II.—*Total Frequencies in Emphasized and Control Groups*

	Before Course. Open	After Course	
		Open	4-way
Frequency of misconceptions—emphasized group ..	180	98	116
Frequency of misconceptions—control group	172	151	169
Maximum possible frequency ..	492	492	492
Expected frequency with random choice of answers	—	—	123
Difference between emphasized and control group $\begin{cases} \chi^2 \\ P \end{cases}$ ..	0·28 >0·5	15·10 <0·001	13·87 <0·001

TABLE III.—*Improvement on Individual Questions Related to Frequency of Teaching of Item*

Treated Group					Control Group				
Question No.		Initial Score	Frequency Taught	Improvement	Question No.		Initial Score	Frequency Taught	Improvement
(a)	(b)	(a)	(c)	(d)	(a)	(b)	(a)	(c)	(d)
A 1	12	34	0	+7	B 1	8	21	75	−6
A 2	6	28	25	+13	B 2	20	31	54	+9
A 3	23	27	38	+23	B 3	24	23	73	+11
A 4	7	22	65	+14	B 4	1	24	0	+5
A 5	2	21	58	+18	B 5	21	21	38	+4
A 6	22	13	8	−5	B 6	18	11	30	−9
A 7	4	12	0	+10	B 7	17	12	8	−5
A 8	5	9	15	+4	B 8	13	9	31	+4
A 9	10	8	52	+6	B 9	16	9	8*	+1
A 10	19	5	58	−7	B 10	14	4	20*	+4
A 11	11	0	8	0	B 11	15	5	42	+3
A 12	3	1	47	−1	B 12	9	2	73	0
Total		180	374	+82			172	452	+21

(a) As in Table I.
(b) Order of presentation to students.
(c) Sum of number of students present on each occasion when item was discussed.
(d) Difference between initial and final frequency observed in open-end test.
* These two items were presented explicitly enough to make their inclusion in the control group questionable.

greater frequency of misconceived answers was to be expected: the number of right answers in this test was also higher, by about the same proportion, than in the open test. The "right" and "misconceived" answers between them attracted nearly all (64.1% and 28.6% respectively) the choices made in the 4-way test.

Relation to Individual Students' Performance

It is also interesting to analyse the results of individual students according to their behaviour during the course. Attendance at lectures and seminars was not formally recorded, but a rough grading was made by asking the teachers to classify their students into frequent, moderate, and poor attenders. The teachers made this classification on two occasions, and were consistent in 32 instances. In the remaining nine the estimates differed by one grade, and these students have therefore been classed intermediately (Table IV). This table shows some notable trends. One is that the students who attended best had, quite unexpectedly, the highest incidence of misconceptions at the beginning of the course. There was, moreover, a moderate but significant correlation ($r = +0.38$, $n=41$, $0.02>P>0.01$) between attendance (scored from 5 to 1 for most to least frequency) and initial number of misconceptions. The second is that the best attenders showed substantial improvement during the course, both on treated and on control items: the moderate attenders improved only on the treated items, and the poor attenders showed little improvement, such as there was being mainly in the treated items.

The difference in improvement in the different groups is highly significant, even without reference to the experimental separation of control and treated items ($\chi^2=33.4$, $n=4$, $P<0.001$). This large χ^2 is largely due to the extreme groups, with excessive reduction in the most frequent attenders and considerably less than expected from the null hypothesis in the two least frequent groups. When the division between emphasized and unemphasized items is taken into account the very uneven partition in the moderate attenders also contributes heavily to the total ($\chi^2=95.7$, $n=9$, $P<0.001$). In interpreting these results it must be remembered that attendance is probably correlated with other qualities, such as intelligence and with private study. No estimates of the amount of private study were made on this occasion, but two estimates of the intellectual performance of the groups are included in Table IV. One estimate is based on the number of right answers given by each student in the final examination of this course; the other is based on a composite mark obtained from examinations held earlier in the course in pharmacology, physiology, and anatomy.

The students who attended most often also had the highest scores on both these assessments of performance, but correlation of the initial score for misconceptions with these measures of intellectual performance is quite insignificant for the whole set of 41 students ($r = +0.138$ with previous mark and $r = -0.003$ with the final exam. mark). That the "best" students improved on both emphasized and control items is not surprising; it is reasonable to regard them as more receptive, or more sensitive, and as responsive to unemphatic teaching as to emphatic. That the "worst" showed least change is corroborative evidence that the experimental procedure is sound: considerable problems would be raised if non-attenders had been much influenced by what happened in teaching sessions. It is the moderate group who are most affected by the form of teaching adopted, and for these students the evidence shows clearly that emphatic pointing out of misconceptions produces much more reduction (55%) in their incidence than does not drawing attention to them (3%).

Students' Attitudes

When tests were given at the end of the course, each student was asked also to award a mark (out of 10) to express (*a*) the use and (*b*) the enjoyment he had derived from various parts of the course. He was also invited to express his own comments, and he was asked whether he was aware of any experiments conducted during the course. Most of the information collected in this way is irrelevant to the present study and will be put forward elsewhere in due course. But two points have immediate relevance. One is that no student reported any awareness of the experiment actually in progress, although several mentioned aspects of the course which differed from those of previous years as possibly experimental. It therefore appears that the methods of teaching adopted in order to emphasize, or avoid emphasizing, misconceptions were not unusual enough to attract attention to any detectable extent. The other

point is that these students had already taken part, during their preclinical course, in an experiment on teaching (Joyce and Weatherall, 1959), and the questionary on use and enjoyment of the course was of the same pattern as the one used in the earlier experiment. The marks awarded in the present course (combined mean=5.0) were consistently lower than those given in its predecessor (mean=7.4), so the results have been obtained with students attending a course about which they were comparatively unenthusiastic.

Many factors could account for the lower ratings given to this course. The outlook of students on the teaching they receive probably changes as their experience grows. The demands of clinical work and of clinical teachers differ from those of the preclinical course, and it was impossible to arrange the course so that students could attend all sessions readily and without distraction. The teachers in this course were with one exception different from those in the preclinical course, and two were new to this medical school and may therefore have evoked different reactions from some students. The students were not aware that an experiment was in progress, whereas their active co-operation had been invited in the preclinical study, and it is possible that disappointment or apathy may have depressed the scores just as enthusiasm about experimentation improves performance (Whitehead, 1938; Houston, 1956; Joyce and Weatherall, 1957). Further experiments are needed to discover whether the students' attitudes are relevant in interpreting the present findings.

Discussion

This paper illustrates a number of points. The first, and perhaps the most important, is that this sort of research is possible. In spite of the large amount of published matter on the subject of medical education very little is based on controlled experiment and nearly all consists of well-considered opinions based on dubiously selected facts (cf. Malleson, 1959). Procedures based on subjective impression may work successfully, but those demonstrated to work by a properly controlled trial are more often reliable, especially if the circumstances of the trial are regarded intelligently and invalid inferences are not applied blindly (Hill, 1960). The same principles can be applied profitably to the critical study of medical teaching as to therapeutic methods; and this study, like its predecessors (Joyce and Weatherall, 1957, 1959), shows that there is no serious obstacle to doing so, at least in a modest way.

Perhaps the most interesting point which emerges from this study is the fact that those students who were the most frequent attenders entered this experiment with the highest incidence of misconceptions and finished with the lowest—that is, the best learners went through a phase of putting forward the selected misconceptions unusually readily. The mechanisms by which students learn are largely unknown and a source of much controversy (Osgood, 1953; Hebb, 1958), and the present observations can perhaps be interpreted in a variety of ways. It is none the less tempting to suggest that these findings point to a trial-and-error mechanism of learning, and lend support to the saying, "If you don't make mistakes, you won't make anything."

The results obtained show a correlation between emphatic warning of possible misconceptions and reduction in the frequency of these misconceptions, mainly in less outstanding students. The results lend no support to the opposite hypothesis that mentioning inaccurate statements leads to their perpetuation. In the circumstances of this experiment, the correlation probably indicates a causal connexion, but it is not certain what part of the process of emphatic warning had the observed effect. The performance of control procedures in an experiment of this sort is difficult, in much the same way as it is difficult to devise a controlled evaluation of psychotherapy (Cole, 1959), and the teachers were at times doubtful whether their method of treating a topic properly belonged to the emphasized rather than the control category of treatments. As the teaching sessions were not recorded verbatim to permit later analysis, the classification has remained with the subjective judgment of the teachers concerned. Possibly emphasis on a misconception led to longer time being spent on the topic than on control items, and the effectiveness of the method depended simply on the extra duration of teaching and not on putting the point negatively. At least the negative presentation has no obvious harmful consequence.

At first sight this knowledge can be applied directly and profitably in improving the technique of a teacher. But there are some pointers towards further knowledge which may go against this simple interpretation. It is notable that those misconceptions which were emphasized early in the course were least affected when tested at the end of the course, and the extent to which emphasis modifies the rate of forgetting facts as well as initial retention has yet to be tested. It is also possible that emphatic teaching, especially of misconceptions, discourages students from hazarding answers of their own when they are unsure of themselves. As Table IV shows, the expression of a large number of misconceptions is in at least some circumstances correlated with learning and assiduousness, and reasons have been put forward why this may be not only a correlate but a cause or means by which skill is obtained. Emphatic teaching may easily slip into dogmatic teaching and discourage students from voicing opinions: it may be better to create opportunities where as many students as possible speculate and discover which of

TABLE IV.—*Frequency of Errors per Student Related to Attendance at Teaching Sessions*

Group	Attendance	No. of Students	Right Answers, Final Score	Previous Examination Results, Composite Mark	Initial Score of Misconceptions	Reduction in Score of Misconceptions		Final Score of Misconceptions
						Emphasized Items	Control Items	
	Maximum score		24	268	24	12	12	24
A	Frequent	5	16·0	163	10·8	+2·8	+3·2	4·8
B	Fairly frequent	5	10·2	146	8·8	+1·4	+0·6	6·8
C	Moderate	15	13·1	145	8·7	+2·7	+0·1	5·9
D	Rather infrequent	4	15·0	143	7·3	+1·8	−0·8	6·3
E	Infrequent	12	12·7	143	7·9	+1·2	+0·3	6·4

their ideas are practical and which are not. These concepts of teaching are themselves susceptible to experimental evaluation, though a larger scale of operations may be necessary than in the present study.

Summary

The value of emphasizing common errors has been examined by a controlled experiment. A short-answer test, containing 24 questions each believed to concern a common source of confusion, was set to a group of students who were part-way through their pharmacology course. From the answers obtained, the topics of the 24 questions were paired according to the frequency with which misconceptions appeared in the students' answers. One topic of each pair was allotted to a treated and one to a control group. For the next four months all teachers emphasized the desirability of avoiding errors in the treated group, while drawing no special attention to those in the control group. The approximate number of student exposures to each topic was recorded. At the end of the course the short-answer test was issued again. On this second occasion the number of misconceptions in both groups was reduced, but significantly ($P<0.001$) more so in the treated group where the errors had been emphasized. Some reasons are discussed for caution in applying these results to the practice of teaching medical students.

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FIFTH INTERNATIONAL CONGRESS ON NUTRITION

[FROM A SPECIAL CORRESPONDENT]

The Fifth International Congress on Nutrition was held in Washington D.C. from September 1 to 7. Judging by the increase in participants compared with the previous congress three years earlier, nutritional research seems to be regaining some of its lost popularity. Press reporters were present in strength, apparently hoping to learn about the treatment of over-nutrition, which they believed was the only local nutritional problem. However, they were disappointed, and what to your correspondent seems as important—namely, under-nutrition—received an adequate coverage in the many discussions.

Lipid Metabolism

Needless to say, lipid metabolism and with it the implication, often unspoken, of a link with arterial (especially coronary) disease has been subjected to a fair amount of investigation. B. BRONTE-STEWART (South Africa) warned, however, of the dangers of a too easy assumption of the hypothesis dietary lipid = lipid in atheromatous plaques = ischaemic heart disease. Though alterations in the serum lipids could be brought about by the dietary fat, it had yet to be shown that such alterations had any bearing on the disease. He pointed out that if the hypothesis were proved then there would be wide implications in the fields of food processing, in health education of the young, and in animal husbandry. Nevertheless, of all the environmental variables of our present-day mode of life only dietary lipid intake could be so closely related to the pathological, metabolic, and epidemiological features of arteriosclerosis. W. S. HARTROFT (U.S.A.) sounded a similar word of caution and advised that the established principles of good nutrition should prevail until the day—far off—when every reasonable doubt of the truth of the dietary fat and arteriosclerosis concept had been removed. He did, however, point out a relationship between the Sippy diet and arteriosclerosis in man. The role of the gut in lipid biochemistry might not be insignificant, according to A. C. FRAZER (Birmingham). Fatty acids could be produced by the intestinal flora and fatty acids could modify intestinal flora. Also pancreatic enzymes could be inhibited by antibiotics with possible effects on lipid absorption.

It is obvious that lipid metabolism must be influenced by the presence or absence of non-lipid substances in the diet. For instance, it was reported by R. E. OLSON (U.S.A.) that the restriction of dietary protein in undernourished populations might play a part in reducing the incidence of atherosclerosis by reducing the concentration of cholesterol and β-lipoproteins in the serum. Evidence is also accumulating of the possibly useful part played by unsaturated fatty acids in the diet, and many consider it desirable that a certain minimum level be maintained in the serum. J. F. MUELLER (U.S.A.) reported that vitamin B_6 (pyridoxine) was essential for maintaining these serum levels.

Evaluation of Nutritional Status

This is a problem which faces not only the individual clinician but also the public health administrator. A panel of experts discussed various methods which included a team recording clinical and biochemical data of large numbers of persons; the study of health, morbidity, and mortality records of a town or country; studying the diet of a community; and the clinical evaluation of an individual with or without supporting biochemical analyses. Improvements in these various techniques were reported, but, as might be expected, no revolutionary methods of assessment were forthcoming.

Nutrition of Mother and Infant

A lively panel discussion on this aspect of nutrition was largely directed to the important problem of mal- and under-nutrition in the tropics. The general view seemed to be that the behaviour of the infant at birth and not its weight should be the index of immaturity (*not* prematurity). D. B. JELLIFFE (Uganda) pointed out that the failure of lactation was not due to bad nutrition, as witness the high incidence of lactation in Africa compared with the United Kingdom or U.S.A.—"more sophistication, less lactation." The question of the value of breast milk as opposed to milk powder in Western countries was discussed at some length with divided views. P. GYORGY (U.S.A.) took a teleological standpoint, and, though admitting that antibiotics could replace the immune bodies, felt that breast milk was at no disadvantage as compared with artificial mixtures. For the undernourished there was no alternative to breast-feeding. Supplementary feeding was stated not to be detrimental at any age, but did it do any good in the very young?

Food Needs and Resources

A symposium on this subject revealed one of the great challenges to nutritional and socio-economic sciences. J. BONNER (U.S.A.) stated that every day 100,000 more persons were present on earth and at the present rate of

increase the world's population doubled itself every 40 years. The birth rate was unchanged and this increase was brought about by longer survival, and he gave as an example the death rate in Ceylon having been cut by half in seven years. In order to keep up the present standard of living, or to raise it, he suggested that there should be fewer children because agriculture could not cope with this rapid increase. Fifty billion people was the maximum the earth could support, and at the present rate of increase this would be reached by A.D. 2100, and even then all deserts must be used for cultivation and there would be no food to spare for any domestic pets. I. K. FOX (U.S.A.), in looking to the future of water supplies, stated that, unlike food, there should be no shortage. He warned, however, against the increasing use of insecticides and the danger that these might be washed into drinking-water. The major nutritional diseases of to-day were seen by H. GOUNELLE (France) to be over-nutrition both in adults and the artificially fed infant and hypervitaminosis A. The main type of under-nutrition he considered to be protein hunger, and again there was mentioned the danger of toxicity from consuming small quantities of additives for long periods.

New Possibilities in Nutritional Research

The panel concerned with this topic were virtually asked to be clairvoyants, and, though to us in Britain the possibilities for future research seem rather limited, it soon became apparent that many avenues remain to be explored. For instance, V. RAMALINGASWAMI said that in parts of India urinary calculi were common, especially in the bladder of young males. The role of vitamin-A deficiency in their production had not been established, but attempts were being made to link nutritional deficiency and the raised serum mucoprotein which often accompanied such calculi. J. H. VAN DE KAMER (Holland), while admitting that much knowledge had been obtained on the malabsorption syndrome, thought much still remained unanswered. The clinical picture of malabsorption might be provoked by a lack of activity of any representative of the fat-, protein-, or carbohydrate-splitting enzymes, an adequate dietary intake thus being prevented from being an adequate nutritional intake. Neuromuscular disease in relation to nutrition was described by E. K. CRUICKSHANK (Jamaica), who divided it into: (*a*) syndromes due to vitamin, protein, and/or mineral deficiencies; (*b*) syndromes occurring in patients with a poor or marginal diet; and (*c*) syndromes where undernutrition influenced the part played by a toxic factor.

General Comment

There were many interesting papers presented in the scientific sections. For example, I. P. BARCHENKO (U.S.S.R.) had found that the nutritional regimen of the mother affected the physical and intellectual development of the child. It was also stated that children in the U.S.S.R. were in good health and the problem of nourishment of Soviet mothers had been solved. Another Russian scientist (A. E. SCHARPENAK) suggested that dental caries was a disease of the whole organism, of multiple aetiology, but chiefly caused by alimentary and neural factors. He advised reduction of dietary sugar and increase of proteins and vitamin B. F. VERZAR, from Switzerland, found that the people in his country who lived above 4,000 ft. had inadequate intakes of vitamins B and C. Rickets was also often seen. This inadequate nutrition was probably due to these folk abandoning their primitive but adequate diet for a more sophisticated but badly balanced diet.

Kwashiorkor, the tropical malnutrition syndrome in children associated with a low protein and relatively high carbohydrate diet, still seemed to be the nutritional disease receiving most attention. Could it be that there was a slight tendency to suspect the role of the dietary carbohydrate in this condition which up to now had been mainly considered as "protein malnutrition"?

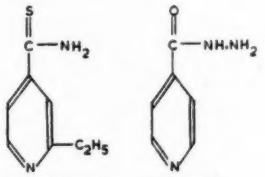
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Ethionamide

"Trescatyl" (May and Baker).

Chemistry.—This drug is 2-ethyl*iso*thionicotinamide, and is related to isoniazid:



ETHIONAMIDE ISONIAZID

Pharmacology.—Ethionamide has twice as much activity *in vitro* against human and bovine *Mycobacterium tuberculosis* as streptomycin, but one-tenth that of isoniazid. In guinea-pigs the effect is similar, but resistance develops with resurgence of tuberculosis towards the 110th day. Combination with streptomycin prevents this. No action against other bacilli except *M. leprosum* has been decribed.

Therapy.—Though a fair amount of work has been done on the treatment by this drug of patients with pulmonary tuberculosis, its place still remains uncertain, though it undoubtedly has a powerful effect on the disease. The following description is therefore unavoidably provisional and tentative.

Primary resistance has rarely been encountered, and, when it occurs, it has been linked with previous treatment with thiosemicarbazone. The natural range of sensitivity has not yet been completely defined.

Cross-resistance to isoniazid, streptomycin, or *para*-aminosalicylic acid has not been found. The drug is supplied in 250-mg. uncoated tablets and is given by mouth in doses of up to 1 g. daily, this being the optimal one. Coated tablets and rectal suppositories have given variable and lower blood levels, and, though they do not induce the gastro-intestinal intolerance often found, should be avoided when possible. Serum levels, even with uncoated tablets, tend to vary greatly. A parenteral form has not yet been prepared.

Ethionamide when given alone to patients has a distinct but temporary effect. Resistance and relapse may emerge within a month, and the drug should never be given alone.[1] French investigations have shown that in combination with daily streptomycin or isoniazid the initial clinical and bacteriological results are very good, but none of these studies have extended over more than three to four months.[1,2] Though ethionamide shows distinct promise, much more extensive trials are necessary to indicate whether it can replace P.A.S. or streptomycin. Even with resistance to two of the standard drugs, the combination of the remaining drug with pyrazinamide is still preferable despite the hepato-toxicity of pyrazinamide, since the very powerful effect of such a combination has been well proved, in contrast to the uncertainty still surrounding ethionamide.

Ethionamide is definitely indicated when resistance to the three standard drugs is present. Tetracycline does not prevent resistance.[3] Trials are still going on in Britain with combinations of cycloserine or pyrazinamide. Perhaps half of the patients treated with either regime have become sputum-negative for *M. tuberculosis*, but conclusions are still premature. At present, it would seem advisable to give ethionamide in doses of 1 g. daily, with both cycloserine 1 g. daily and pyrazinamide 40 mg. per kg. body weight

daily, perhaps with viomycin 2 g. twice weekly in addition. Probably the therapeutic effect of such a multiple combination is greater than that of two alone, though toxicity may be greater. In a few patients treated in this way results have been impressive. Surgery at the optimal moment should always be considered. The duration of drug treatment should be at least 18 months.

In extrapulmonary tuberculosis the place of ethionamide has been little investigated.

Side-effects.—The commonest are anorexia, nausea, and vomiting, abdominal discomfort, and diarrhoea. These may be avoided by lowering the dose to 0.5 g. daily, but this dose should always be supplemented by rectal administration of ethionamide, since present evidence indicates that this dose may be too low to avoid resistance emerging, at least to pyrazinamide. Sometimes, if the dose is started at 0.5 g. daily and slowly built up to 1 g. over 10 to 14 days, these symptoms may be avoided. Rarely, headache, depression, acne, and exacerbations of isoniazid-induced peripheral neuritis have been described.

N.H.S. Basic Price.—100 250-mg. tabs., 105s.

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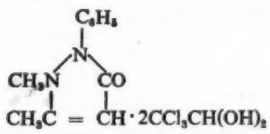
2 Véran, P., Moigneteau, C., Trichereau, R., and Rist, N., *Rev. Tuberc. (Paris)*, 1959, 23, 454.
3 Somner, A. R., Ross, J. D., MacLeod, H. M., Stewart, S. M., Horne, N. W., and Crofton, J. W., *Brit. med. J.*, 1959, 1, 486.

Dichloralphenazone

"Welldorm" (Smith and Nephew).

Chemistry.—This is a molecular complex of chloral hydrate and phenazone and has the following structural formula:



Pharmacology.—Its main action is that of a hypnotic, but the phenazone may have a slight antipyretic and analgesic effect. Animal experiments show that its acute toxicity is that of chloral hydrate. Chronic toxicity tests failed to show any adverse effect.

Therapy.—Dichloralphenazone tablets, 10 gr. (0.65 g.), are used for the treatment of insomnia. The suggested dose is 2 to 4 tablets for adults. Tablets of 2½ gr. (0.16 g.) are available also, and 2 to 3 tablets are suggested for children of 3–6 years. They are taken crushed in water and have the advantage over chloral in lacking the nauseating taste of that drug. They are not addictive, constipating, or liable to cause hang-over.

Toxicity.—Neither chloral hydrate nor phenazone (antipyrine) is likely to produce untoward effects. Rarely skin rashes arise from one or other drug. Agranulocytosis from phenazone is extremely rare.

N.H.S. Basic Price.—10-gr. tabs., 12 for 1s.; 2½-gr. tabs., 12 for 6d.

During the first seven months of the year the British Red Cross Society has arranged 4,844 training courses for its own members, the National Hospital Service Reserve, workers in industry, and for the general public. Of the thousands who have attended them, 28,708 adults and 26,493 young people (including many entering for the Duke of Edinburgh's Award) have gained certificates. This is an increase over the 1959 figures of 5,243 and 3,797 respectively. Two hundred and ninety-two instructor's certificates for first-aid, nursing, and mothercraft have also been issued. This is an increase of 34 on last year.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Virus Strains for Live Polio Vaccine

SIR,—I feel that the medical profession is entitled to a more accurate analysis of the current status of live virus vaccines against poliomyelitis than it could derive from the announcement made on August 24 by the Surgeon General of the U.S. Public Health Service endorsing only the set of strains developed by Dr. Albert Sabin as acceptable for licensing (see *Journal*, September 3, p. 746).

The decision, we are told, was based on a lesser degree of neurovirulence in monkeys for the Sabin strains as compared to the other candidate strains in tests performed by the Division of Biologics Standards of the National Institutes of Health. The following table

Monkey Neurovirulence of Type 1 Strains

Route	Vaccine	Testing Laboratory	Dose of Virus Inoculated (PFU*)	Clinical Signs	Histologic Lesions		
					L	*C*	*BS*
Intracerebral	Koprowski	Div. Biol. Std.[1]	7·6	0/5	2/5		
			6·6	0/5	2/5		
			5·6	0/5	2/5		
			4·6	0/5	2/5		
			3·6	0/5	0/5		
			2·7	0·5	0/5		
	Sabin	,,	7·4	0·9	0/9		
			6·4	0·4	0/4		
			5·4	0/5	0/5		
			4·4	0/3	0/3		
			3·4	0/3	0/3		
	,,	Div. Biol. Std.[2]	7·4–7·7	0/3	0/3		
	,,	Melnick[3]	Undil.	0/12	1/12		
			10^{-1}	1/7	1/7		
			10^{-2}	1/7	1/7		
Intramuscular	Koprowski	Div. Biol. Std.[2]	7·7–7·9	2/4	2/4	1/4	2/4
			6·7–7·2	0/12	1/12	1/12	1/12
			6·2–6·4	0/2	0/2	0/2	0/2
	Sabin	,,	8·7–8·9	0·4	3/4	0/4	0/4
			8·7	0/3	3/3	2/3	2/3
			7·7–8·7	0/5	4/5	1/5	3/5
			7·9	0/14	5/14	2/14	1/14
			6·7–7·2	0/4	0/4	0/4	0/4

* Plaque-forming units in log to the base of 10.
L=lumbar enlargement of cord; *C*=cervical enlargement of cord; *BS*=brain stem.

[1] Murray, R., *et al.* Comparative virulence for rhesus monkeys of poliovirus strains used for oral administration. Pan American Health Org. Scientific Publication No. 44: 39, 1959.
[2] Kirschstein, G., *et al.* Neurovirulence after intramuscular inoculation of monkeys. Pan American Health Org. Scientific Publication No. 50: 90, 1960.
[3] Melnick, J., *et al.* Studies on live poliovirus vaccine: Its neurotropic activity in monkeys and its increased neurovirulence after multiplication in vaccinated children. *J. Amer. med. Ass.*, 1959, 171, 1166.

summarizes published results of neurovirulence tests in monkeys injected either intracerebrally or intramuscularly by the personnel of the Division of Biologics Standards of the National Institutes of Health, U.S. Public Health Service, with the Sabin and Koprowski type 1 strains. The same table also shows comparative results obtained with Sabin's type 1 strain injected into monkeys in Dr. Melnick's laboratory in Houston.

Of 30 monkeys injected intracerebrally with the Koprowski strain, none showed clinical signs and eight showed histologic lesions of the central nervous system. None of the monkeys injected by Division of Biologics Standards personnel with the Sabin type 1 strain showed either clinical signs or lesions, but three out of 26 monkeys injected with the same lot of Sabin's vaccine by Dr. Melnick showed lesions of the central nervous system and two showed *clinical signs*. Of 18 monkeys injected intramuscularly with the Koprowski strain,

two showed clinical signs and one more animal had central-nervous-system lesions. Of 30 monkeys injected by the same route with Sabin's strain, 15 showed lesions of the central nervous system and in six the lesions spread to the brain stem. Since none of the 30 monkeys showed clinical signs, choice of Sabin's type 1 strain as a reference strain was accompanied by the requirement that no paralysis should be observed after intramuscular injection, but no mention was made of lesions of the central nervous system. It can be easily argued that lesions observed in the brain stem after intramuscular inoculation are as indicative of residual neurovirulence as actual paralysis. Ignoring these facts might be taken to indicate that the monkey safety standards were picked to fit a particular strain and not the strain to fit the standards.

The Surgeon General qualified his choice of Sabin's type 3 by referring to its relatively poor immunizing properties and to the fact that it changes in neurovirulence for monkeys after one passage through man. The Koprowski type 3 vaccine has better immunizing properties and is identical with the Sabin type 3 vaccine after passage through man. It is therefore difficult to understand why the Sabin type 3 vaccine was the only type 3 strain approved. In addition, since all the vaccines tested in monkeys had probably been contaminated with monkey virus (vacuolating virus), it would be dangerous to make any generalization until it can be proved in what way such an agent has affected the results of the neurovirulence tests.

The safety of the Koprowski strains has been demonstrated by administration without any ill effects to over nine million people. This is direct evidence of safety. The results of neurovirulence tests in 131 monkeys is evidence (rather inconclusive evidence in this case) only of how the test monkey responds to each individual strain which has already been shown to be safe for feeding to susceptible humans. The test in monkeys should be a valid test to establish and check the permanence of the seed strains from time to time. Comparison with an N.I.H. reference strain is also a means of determining strain neurostability. Neither test directly measures safety in humans.

Although it is a step forward that the principle of live virus immunization in poliomyelitis has at last been officially accepted, I am taking strong exception to this exclusive endorsement of one set of strains. In my opinion, such an endorsement should evoke a protest from individuals who believe that fair scientific judgment should be the basis for decisions affecting the physical welfare of man.—I am, etc.,

Wistar Institute,
Philadelphia 4, U.S.A. HILARY KOPROWSKI.

Prognosis of Eczema-asthma Syndrome

SIR,—I read with great interest the article by Drs. D. Burrows and R. W. B. Penman (September 17, p. 825) and congratulate them on presenting these further facts on this subject. The results they present give an even gloomier picture than our own.[1] The cases we followed up had also been admitted to hospital; a point which we stressed and which Drs. Burrows and Penman clearly draw attention to. For every case severe enough to warrant admission to hospital there must be a very large number of cases of infantile eczema which are milder, and the prognosis in these cases is good and the majority clear by the age of 2–3. This is perhaps an obvious point, but I would like to draw attention to it as I fear that many parents reading or hearing about the article may assume that there is only a 20% chance of their child getting rid of the eczema before the age of 10–13 years, and not realize that this depressing outlook applies only to infantile eczema of a very severe grade.

Infantile eczema is a very common condition. In the Bristol area over 3% of the general population have it, in a degree requiring medical attention[2]; although this figure was lower in a survey in the Cambridge area.[3] However, in milder grades it is much more common than this, and if we include infants with slight transient eczema we gradually move towards "normality." I believe that there are all grades of ease with which the skin is eczematized (sensitivity), ranging from "normality" to infants who have mild transient eruptions, and on to the more severe grades of eczema. From birth to adult life there is a progressive tendency for the skin to become less easily eczematized (sensitive), and because of this in most cases the eczema gradually settles down. Adverse influences can act against this progressive improvement and include psychological stress and insecurity. In the occasional case of the child starting with eczema at a later age, presumably the sensitivity of the skin has only increased to an active eczema level because of the development of such adverse factors.

I find it impossible to separate out patterns of eczema in infants. What most dermatologists mean by seborrhoeic eczema in infancy is presumably a particular distribution of eczema involving the scalp, behind the ears, axillae, and groins, but I commonly see almost every combination of eczema in these sites associated with the usual infantile eczema involving the face and limb flexures, at the same time or at a later date. However, I do not want these views of mine, which may not be generally accepted, to detract from the main point I would like to draw attention to, that in spite of the very bad prognosis of the more severe cases of infantile eczema most of the common minor grades clear very satisfactorily with time.—I am, etc.,

Bristol. ROBERT P. WARIN.

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[1] Vowles, M., Warin, R. P., and Apley, J., *Brit. J. Derm.*, 1955, **67**, 53.
[2] Walker, R. B., and Warin, R. P., ibid., 1956, **68**, 182.
[3] Brereton, E. M., Carpenter, R. G., Rook, A. J., and Tyser, P. A., *Med. Offr*, 1959, **102**, 317.

Soap and the Skin

SIR,—Some of the statements made by Dr. F. Ray Bettley in his article on "Some Effects of Soap on the Skin" (June 4, p. 1675) cannot in my opinion be allowed to pass unchallenged. The definition of soap is usually accepted as the combination of a fatty acid with an alkali or other metal. In industry, where one is likely to meet chemical compounds more than in hospital practice, there are many of these compounds in use, and I cannot recall any case of dermatitis in a reasonable experience of industrial medicine as a full-time medical officer, consultant, and also as witness in quite a number of legal actions.

Examples of soaps amongst many others used in industry are copper, aluminium, and calcium stearates. Soaps are used in dental and hair preparations, and, although it seems hardly necessary to mention it, in vanishing and other cosmetic creams soaps are usually included. It would therefore appear that a large number of persons in industry and elsewhere are at risk if soaps are likely to aid absorption of other materials.

It is difficult for me to correlate Dr. Bettley's statement (p. 1677) that he used a mixture of 5% toilet soap and 5% pure potassium palmitate for cleansing the skin in eczema, seborrhoeic dermatitis, and psoriasis without "any irritant property in the soap except in contact with ulcerated surfaces" with one of his conclusions: "Thus the presence of soap may be a more important factor in producing irritation

than these various additives which are often blamed. Brain,[1] also quoted by Bettley, stated that: "The reported chemical and biophysical hazards of using common soaps fall into a proper perspective if one considers how often tablets of this alkaline irritant are rubbed into the hands with impunity, and even delicate skins tolerate the sparing use of a good toilet soap. Many patients with skin diseases tolerate and often benefit from the cautious use of soap and water."

It is on the subject of soap containing barrier creams that I consider the statements made and theory expressed, and the conclusions drawn, are not borne out by practical experience. In two industrial organizations with which I have been connected for some twenty years hundreds, possibly thousands, of chemicals have been in use. Many of these are volatile. As there is presumably a residue of soap left on the skin of hands and face after washing, some cases of absorption of these active chemicals should have occurred; at least there should have been some cases of dermatitis. In general, it is true to state that this does not occur. Occasionally volatile chemicals do attack the skin as primary irritants, and this is quite independent of washing or any possible soap residues left on exposed skin.

Barrier creams containing soap in one form or another are in common use in this country and in America for industrial purposes in dry working conditions and for which they are appropriate. I have endeavoured to establish how much of this type of barrier cream is in actual use. Two leading manufacturers have given me estimates of the amount sold in the past ten years. Between them they conservatively estimate that at least five thousand million applications of barrier creams containing soap have been made during this period, and there is no reason to believe that harm has resulted or evidence that they have caused toxic absorption or increased the risk, nor that they have contributed to penetration of the skin. A recent report by Vinson and Choman[2] is of considerable interest in this context, since the authors, after investigation, exonerated soaps of any absorption or penetration into the skin, and report that a soap solution at a level of 8% in conjunction with nickel sulphate did not elicit a nickel response, although other surface-active agents, particularly sodium lauryl sulphate, provoked the eczematous reaction associated with nickel and caused its deep penetration into the skin.

There are, however, some groups of chemicals with which the injudicious use of barrier creams may play a part in absorption. These are nitro-bodies and organo-phosphates, and in such cases no fatty substances should be used in the barrier creams. I have always found that industrial physicians and works' chemists are well aware of the risk of highly liposoluble compounds, and the processes are generally totally enclosed and absorption, if any, is usually the result of accident.

Dr. Bettley considers that the effect of ethanolamine in soaps may raise problems in potentiating other industrial irritants. The B.P. Codex Revision Committee has published formulae for barrier creams. In two of these creams (the dust- and water-repellent barriers) triethanolamine is included. In the skin-conditioning cream formula recommended by the committee, triethanolamine ricinoleate 1% is the emulsifying agent. Triethanolamine, a known irritant, was not the best of choices, as in the annotation, "Hazards from Cosmetics,"[3] you drew attention to "dermatitis of the hands apparently caused by the synergistic action of household detergents and triethanolamine in a hand lotion" (Thyresson *et al.*[4]). Alberman,[5] commenting on this, drew attention to the danger of inclusion of the triethanolamine in barrier creams and stated, "It would appear that the hazard is at its maximum with a barrier cream intended to be applied before work rather than a hand-conditioning preparation, since in the former case the detergent and triethanolamine will be present together in the skin for the maximum time."

There would appear to be other emulsifying agents available less likely to cause trouble. Whilst as yet there is no perfect single barrier cream with or without soap against all known irritants, progress is being made and it is now possible to provide a cosmetically acceptable barrier cream giving considerable protection for a reasonable period against strong acids and alkalis, neat and soluble cutting oils, hydrocarbon solvents, glycols and their compounds, resins and catalysts, phenolic paint-strippers, and detergents. It will be realized that in these groups of chemicals there are strong possibilities for percutaneous penetration and absorption, but my personal experience is that the claims made for the creams are justified. I also agree with Dr. Bettley's report that "the effect of alkali alone in the *p*H range of soap solutions is negligible," but I could go further, as I consider that the *p*H range of barrier creams, including those with a soap base, do not give rise to any difficulties.

In industry, theoretical considerations do not always apply, and, as Dr. Bettley admits, "The test of usage—the chief evidence upon which we can rely," is the one upon which we must accept conclusions, and, as soap-based barrier creams are still being used by thousands of workers daily without trouble, there would appear to be no evidence that their use is inadvisable.—I am, etc.,

London W.1. L. B. BOURNE.

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2. Vinson, L. J., and Choman, B. R., *J. Soc. cos. Chem*, 1960, **9**, 127.
3. *Brit. med. J.*, 1958, **2**, 38.
4. Thyresson, N., Lodin, A., and Nilzen, A., *Acta derm.-venereol. (Stockh.)*, 1956, **36**, 355.
5. Alberman, K. B., *Brit. med. J.*, 1958, **2**, 328.

School Phobia

SIR,—The very timely leading article on school phobia (September 17, p. 848) calls attention to recent literature on this subject, and immediately the subject once again became the source of comment in the lay press. There is a certain wonderment that such simple measures as "a box on the ear" is not the recommended treatment. Some confusion still exists between truancy, which is voluntary and produces satisfaction, and what has been called "school phobia," which is much more obscure, even to the participants.

The distress of the child patient is certainly no fit subject for the so-called humour of many lay commentators, and its treatment is never so simple nor so effective as it might appear to those who view the problem against the backgrounds of recollections of their own somewhat legendary childhood. The social background and precipitating factors, and the psycho-pathology of individual cases, all need to be studied in each patient as an essential part of treatment. A wider problem, however, still exists. Granted that "school phobia" can be looked upon as a particular example of separation anxiety, the question arises, nevertheless, as to the basis for the choice of this particular behaviour as the outward expression of the disturbance.

School attendance is a community issue as well as an individual obligation. Failure to attend school reflects attitudes to authority. In cases of school phobia, attempts to enforce school attendance produce panic states of almost psychotic intensity against which all authority is helpless. In my paper[1] I ventured the suggestion that cultural factors were equally as important as the aspects of the child–parent relationship. Parents pass on their values to the child, but rapid cultural and technical change has made parents uncertain of what it is that they have to pass on. There is a need for sociological as well as psychological studies into the concepts that fathers, mothers (and teachers)

have of their respective roles, and the subject is no less a one than the problem of integrating the individual into the community.—I am, etc.,

London N.W.3. J. H. KAHN.

REFERENCE

[1] Kahn, J. H., *Med. Offr*, 1958, **100**, 337.

SIR,—I read your leading article on school phobia (September 17, p. 848), in which you say: "Ultimately, if it is felt that the home background is going to remain unsatisfactory, it may be better for him to go to a boarding-school, *if the parents can afford it.*" (My italics.) Berkshire Education Committee awards grants to parents, according to income, if there is any special need for their children to attend boarding-schools. If a boarding "special school" is needed, the local education authority will pay the fees without regard to income. Do not other authorities do the same thing?

Sometimes it is difficult to find a suitable school, but surely financial considerations should not come into it. —I am, etc.,

Oxford. MARY WATSON.

SIR,—Your leading article (September 17, p. 848) is most helpful and clarifying. I particularly welcomed the emphasis laid on the severe and tortuous emotional difficulties from which the mothers of these children tend to suffer. Your reminder that they should be helped rather than blamed cannot, I think, be made too strongly, the more so because these mothers are so often the kind of gentle, timid, foolish people who are sitting targets for the scorn of neighbours, school welfare officers, and society at large.

I think that one important correction of fact must be made: you remark that these children might benefit from boarding-school "if their parents can afford it." Under the Education Act of 1944 the question of payment need not arise, because the local education authority has a duty to provide appropriate residential schooling for any child who is considered by a psychiatrist to be in need of it by virtue of being psychologically "maladjusted."

Experience has proved time and again that children with school phobia attend school happily when in hostel or boarding-school; and, provided that sufficient skilled help is available to meet all the family upsets precipitated by the idea and fact of separation, this is, in my experience, often far the most helpful solution to the problem.

Needless to say, boarding-school should not be suggested in the early case, before the possibilities of a simpler and cheaper solution have been explored. Neither should the suggestion ever be made as an open or veiled threat in order to compel school attendance: this is commonly and easily done, and among other drawbacks tends to make the child associate the idea of boarding-school with prison. On the other hand, the suggestion should not be delayed until the difficulty is firmly established and entrenched, but in good time while all the family are still desperately trying to combat the trouble and who will therefore most probably provide the co-operation essential for the scheme. It should also be borne in mind that available schools are not necessarily ones for maladjusted pupils only, which many parents associate with crank teachers and bizarre pupils. Many good independent schools have a few places available for local education authorities for children of this kind.

I am not suggesting that this is necessarily the only solution in all cases, nor yet the ideal one. Each case must be considered on its merits. But one of the serious limiting factors will for a long time remain the grave shortage of psychiatric and other staff equipped to provide the intensive psychotherapy that is usually what these patients and parents most need.—I am, etc.,

Child Guidance Clinic, Chislehurst. JUDITH WATERLOW.

SIR,—Does your leading article (September 17, p. 848) really represent the current medical opinion on this subject? Why is it useless and indeed harmful to blame the mother? True it is also the father's responsibility, but if they are not responsible for the management of themselves and their child, who is? Is it the Queen of Sheba, or the monsoons? Is no one to be blamed for failing in their responsibilities? Should no one be expected to exert any self-discipline? I wonder what view St. Peter will take when we come to the gate. Meantime, what lead ought we to give to the public?—I am, etc.,

Wittersham, Nr. Tenterden, Kent. G. C. MILNER.

SIR,—Though welcoming the interest shown in child psychiatry by your leading article on school phobia (September 17, p. 848), I feel it gives a rather misleading picture. It is stated: "School phobia is a misnomer . . . and that it is really a form of separation anxiety." But this is substituting one symptom for another and not adding anything to our understanding, and it is perhaps this stress on separation which distorts the picture. J. P. Nursten[1] is quoted as finding "a high incidence of prolonged separation from parents in early years." The perusal of the article referred to does not show this, and many writers have stressed the absence of any such separations. The important role of the mother is recognized, but one is on the whole left with the impression of a rather silly, doting mother and an obstinate child who "digs his heels in and flatly refuses to go."

No one who has seen a case of school phobia can fail to be impressed by the child's immense fear merging into panic, and often associated with pallor, sweating, and near collapse, when an attempt is made to get him to school. The fear is irrational and springs from an inner conflict and cannot be dealt with by discipline or argument. Many of these cases are severely depressed and the onset of symptoms often occurs after a death or severe illness in the family. The relationship between mother and child is essentially ambivalent and the clinging and over-concern which they show for each other is a protective mechanism necessary to counteract the concomitant feelings of hostility. Many of these children stay off school because they are afraid the mother will die or commit suicide during their absence. I fully endorse the necessity for early treatment and the need to keep the child at school for at least part of the day, as far as possible. But to suggest that "the worst thing the family doctor can do is to give permission for the child to stay at home until such time as the psychiatrist can see him" is, I think, a dangerous precept. In severe cases it is not possible to get the child back, and unsuccessful attempts at forcing only augment the symptoms and make subsequent treatment more difficult. Where it is obvious that the child is too severely disturbed to return it may be of great help to the family if their guilt is reduced by permission to stay at home until further help can be given.

Most clinics regard these patients as urgent cases and give them priority, but lack of time and staff does sometimes make this difficult. I cannot agree that clinics are "so cluttered up with simple cases referred by school medical officers which could have been perfectly well dealt with by a paediatrician." Where school medical officers are unable to deal with the case themselves it is unlikely that a paediatrician, who has no training in child psychiatry, will be able to offer any more. Our constant plea is to be sent the simple early cases at a stage when they are most readily treatable and before they have become the complicated and often intractable cases through years of delay which we are usually asked to treat. This applies particularly to adolescents, who are notoriously difficult to treat because of the drive for independence from adults which is characteristic of their age, and often because the time available before they leave school is inadequate for treatment. Fortunately the majority of school phobia cases occur about 11 with the change from junior to senior school and have not yet entered adolescence.—I am, etc.,

Child Guidance Training Centre, London N.W.1. SUSANNAH DAVIDSON.

REFERENCE

[1] Nursten, J. P., *Med. Offr*, 1958, **100**, 340.

SIR,—I read with interest your leading article on school phobia (September 17, p. 848), as I recently carried out a study on this subject in the children's department of the Maudsley Hospital.[1] Using statistical techniques, 50 cases of school-refusal were compared with equal numbers of truants and randomly selected controls.

The findings are in some instances at variance with points made in your article. In the investigation it emerged that, contrary to clinical impression, school-refusal is not significantly more frequent in only children, in youngest children, or in children separated by a gap of at least five years from the next oldest sibling. Children with these symptoms are on the average more intelligent than truants, but they do not differ significantly from controls. Furthermore, they appear to have had significantly less experience of maternal and paternal absence before the age of 5 years and of maternal absence after the age of 5 years than either truants or controls.—I am, etc.,

Child Guidance Training Centre, London N.W.1. L. A. HERSOV.

REFERENCE

[1] Hersov, L. A., *J. Child Psychol. Psychiat.*, 1960, **1**, 130 and 137.

Child Psychiatry

SIR,—Dr. B. K. Attlee (September 3, p. 737) and Dr. Freda Reed (p. 738) draw attention to the help that married women doctors with children of their own might give in the field of child psychiatry. However, they go on to point out the difficulties of obtaining the D.P.M. and the "rigorous training" that goes with it, "which includes a full-time year in a mental hospital," and if it were not for this, many of these women might well like to take up this work in the capacity of part-time clinical assistants.

Valuable as personal experience of bringing up children is—and the practice of child psychiatry certainly needs a facility for understanding and handling children—it also requires the acquisition of diagnostic acumen and clinical judgment, to weigh up the psychiatric or general medical problems presenting in the child in the setting of the family. The family includes parents and maybe other adults, the assessment of whose mental state or psychological abnormalities may be highly relevant for the diagnosis and treatment of the family as a whole and for the child in particular. The child-psychiatrist thus can hardly fulfil his responsibilities without an adequate knowledge of adult psychiatry, which requires a sufficient length of training in that field as well as in child psychiatry.

Dr. Reed offers a possible solution to their problems by suggesting that training in child psychiatry might be modified by allowing such a candidate to take a part-time post in a psychiatric hospital and later in a child-guidance clinic, the two years in such a post being equivalent for examination purposes to one year in a full-time post. If this proposition is practicable for mental hospitals and child-guidance clinics, which undertake training, and they are able to offer facilities for part-timers, it might then profitably be considered by the examination authorities. However, such a candidate, although presumably fairly senior in years, will need the patience to remain in a junior position for double the normal time to ensure herself an adequate training.—I am, etc.,

West Wickham, Kent. W. WARREN.

Student Health Services

SIR,—"We hold the view that universities have responsibilities in respect of the health of their students and that for the fulfilment of these responsibilities each should provide a properly organized student health service." These words were written in the Goodenough Report on Medical Education which appeared in 1944, and your annotation "Second Growth of Student Health Services" (September 17, p. 851) is a timely reminder of the slow growth of student health services at a number of universities in this country. It is encouraging to learn of recent improvements. Little mention was made, however, of those universities—chiefly in the provinces—where progress has perhaps been less hampered by academic indecision or indifference. The annotation also conveys a somewhat restricted picture of the scope and nature of student health work in general.

At many centres preventive aspects are still regarded as important. For example, chest radiography of tuberculin-positive reactors, programmes of vaccination and immunization, the supervision of environmental hygiene (e.g., radiation hazards, prevention of accidents in workshops and laboratories, regular examination of food handlers, etc.), and health education are student health activities all of which lie within the preventive field. The value of the routine examination is perhaps more controversial and seems to depend largely on the personal convictions of the examiner. Possibly it is the word "routine" that is misleading, with its implications of stereotyped form-filling and purely physical examinations of the "short sight"/"flat foot" variety which have an admittedly limited place in student health practice. The procedure might have proved more rewarding and less of a chimera if the right questions had been asked. In the University of Wales these examinations are still regarded as a valuable screening device, provide the basis of much of the clinical work of the service, including the identification of a fair amount of psychiatry of the kind your annotator describes, and do not appear to diminish in usefulness. A voluntary annual attendance by some 95% of new students during the past five years does not indicate the development of consumer resistance.

It is, as your annotator suggests, essential to provide facilities for clinical care, but there is room for difference of opinion as to how this can best be achieved to

meet prevailing local needs. In this university the trend has been towards the development of a *university* service of "occupational" type, analogous to the services found in enlightened sectors of industry and commerce. This has already led to the provision of two new college health centres housed in student amenity buildings and each designed to serve populations of 2,500–3,000. College nursing services are an additional development. No doubt medical officers at other provincial universities could also record the gradual expansion of their facilities, though possibly along different lines. At all events it would be erroneous of university administrators to infer that the provision of psychiatric help, important though this is (and it is certainly better than nothing), is quite the same as the development of health services adequate to the requirements of our expanding universities.—I am, etc.,

GRAHAM GRANT.

University of Wales Student Health Service,
Cardiff.

SIR,—In your annotation on the "Second Growth of Student Health Services" (September 17, p. 851) it was pleasant to read approval of the clinical facilities, especially of a psychiatric kind, that are being developed for students. But the final paragraph does not do justice to the London School of Economics and the London University Institute of Education.

The psychiatric advisory service at the London School of Economics was started as a research project from the Bethlem Royal and Maudsley Hospitals in January, 1952, and was, I believe, the pioneer of this kind of service in the country. A report of its work was published after 18 months.[1] In April, 1953, the London School of Economics contributed to the financial support of the venture, and in November, 1954, the Institute of Education started a similar service which could at that stage be run concurrently. In October, 1957, the enterprise was so successful that both schools took over the full responsibility for these services. In October, 1958, there was so much work to do that the L.S.E. service became a full-time one; that at the Institute of Education carried on as before, but in other hands. In view of this history it is hardly fair to mention these two schools directly after a remark about "the laggards" of London University, even if the implication is quite unintentional.—I am, etc.,

J. C. READ.

The London School of Economics
and Political Science,
London W.C.2.

REFERENCE

[1] Read, J. C., *Lancet*, 1954, **1**, 822.

Lumps in the Breast

SIR,—Surgical dogma is always dangerous. Mr. Brian McN. Truscott and Dr. D. G. Bratherton may rightly have stated that the treatment of a lump in the breast is to remove it (September 17, p. 857), but if there was any condition in which it was more important to treat the *patient* than to treat the lump, breast disease is the best example. There are exceptions to hurried surgery. Infected cysts and advanced neoplasms cannot be blindly subjected to excision. The statement is as dangerous and as impossible to pursue as to claim that *every* lump in the thyroid should be treated similarly. Let us not retreat to the era in which bilateral mastectomy was the treatment for cystic mastitis. We must continue to treat the *patient*. Experience alone will dictate the wisdom and the moment of excision.—I am, etc.,

D. F. ELLISON NASH.

Dulwich,
London S.E.19.

SIR,—I never thought that I should ever see in a scientific journal such a letter as that headed "Lumps in the Breast" (September 17, p. 857). In it the whole of the general practitioner section of the profession is stigmatized as fools and indeed criminals. It is impertinent because on the flimsiest evidence it makes a wild accusation; it is unscientific because it accepts third-hand hearsay as fact; it is stupid because it raises grave doubts whether posts of scientific importance are held by the right people. Although an apology and withdrawal would seem to be indicated, I doubt whether even this would allay the indignation felt by many of my fellow G.P.s.—I am, etc.,

DAVID BROWN.

Liverpool 20.

Psychotic Reactions and Phenelzine

SIR,—I would like to confirm the cautionary observations of Dr. J. Johnson and Dr. M. D. Eilenberg (September 17, p. 857) about the possibility of psychosis following the use of anti-depressive drugs, both monoamine-oxidase inhibitors and "tofranil" (imipramine). In a current series of hypomanics, two cases have occurred after receiving "niamid" (nialamide), one after "nardil" (phenelzine), and two after imipramine. It is interesting to note that the acute phase began within one week in three cases, within two weeks in the fourth, and at an uncertain point within seven weeks in the fifth. The hypomania has persisted for up to three months after the withdrawal of the anti-depressive drug. Three of the patients had previously suffered from mania or hypomania; all but one patient had a positive family history of depression. I would like to quote one of the cases in more detail.

A 66-year-old female who was admitted to hospital at the age of 50 with a severe depressive illness and had been there ever since. She displayed episodic swings between depression and mania, each phase being of about 2–3 months' duration. However, before the present episode she had been chronically depressed for five years. On June 1, 1960, she received nialamide, 100 mg. thrice daily. On June 3 reserpine 0.5 mg. thrice daily was added. On June 4 the patient became frankly hypomanic and almost immediately went into mania. She continued thus for some weeks after the withdrawal of both drugs. The family history was positive; the father committed suicide.

This case is of particular interest in that mania occurred following a five-year episode of depression three days after beginning nialamide and one day after beginning reserpine. Brodie and Shaw[1] have described this effect with iproniazid and reserpine. It is suggested that the former allows an accumulation of 5-hydroxytryptamine to an inhibitory concentration; inhibition of a sedating system leading to excitation. Reserpine is said to enhance the effect by releasing 5-hydroxytryptamine from its binding sites.

I would suggest that the use of anti-depressive drugs in known cases of manic–depressive psychosis is not without its dangers, particularly in general practice and out-patient work. It is notoriously difficult to manage hypomanics outside the hospital.—I am, etc.,

B. G. GRADWELL.

Holloway Sanatorium,
Virginia Water.

REFERENCE

[1] Brodie, B. B., and Shore, P. A., *Ann. N.Y. Acad. Med.*, 1957, **66**, 631.

Side-effects of Phenelzine

Sir,—I read the letter by Dr. J. Johnson and Dr. M. D. Eilenberg (September 17, p. 857) on the psychotic effects of phenelzine ("nardil") and imipramine ("tofranil") with great interest. I would like to draw attention to some physical side-effects of these two drugs, as did Dr. J. Clarke (April 16, p. 1204). In ten cases of recurrent endogenous depression that we have treated here, there have been marked physical side-effects of hypotension during treatment with phenelzine at a dosage of 45 mg. daily. Six of the patients here felt giddy and had fallen, even on getting up slowly from a resting posture. One patient, who had a normal blood-pressure of 130/80, had a blood-pressure of 80/60 after four days' treatment with phenelzine. Other patients had a corresponding fall in blood-pressure.

After the first reports of giddiness, we began taking the blood-pressures at four-hourly intervals, in the prone, sitting, and erect positions. We found that there was considerable fall in the blood-pressures on standing. In two patients bed-rest alone for a week did not elevate the blood-pressure significantly. We put one patient on dextro-amphetamine sulphate, 5 mg. morning and noon, and the other on "methedrine" (methylamphetamine hydrochloride), 5 mg. morning and noon. In the latter patient we also gave "D.O.C.A." (deoxycortone acetate), 2.5 mg. every other day. The combination of these two drugs raised the blood-pressure sufficiently for these patients to be ambulant.

The two patients who fell down due to giddiness on several occasions were in the age group 60–65, and it was considered that the cerebral blood-flow had been reduced by the fall in blood-pressure. We did not withdraw phenelzine from them, or the other eight patients, as they were making such good progress and they, in fact, made a complete recovery from a quite severe depression. Only two patients needed three electro-cerebral treatments as a supplement to complete their remission.

One further case which shows the dangers of not average but overdosage of a combination of phenelzine and imipramine was a girl of 23 years who was addicted to "preludin" (40 tablets a day). In the course of three weeks she was weaned on to chlorpromazine, 50 mg. four times a day, and discharged home. She suffered some reactive depression due to withdrawal of preludin. She was therefore given phenelzine, 15 mg. three times a day, instead of chlorpromazine. She was advised, by another opinion, that if the phenelzine did not lift the depression in 21 days, to add imipramine, 25 mg. three times a day. She took about 200–300 mg. of imipramine, with the following result: she developed (1) profuse sweating, (2) extreme restlessness and hyperexcitability, (3) collapse, followed by (4) death in hyperpyrexia (temperature 109° F. (42.8° C.)) four hours after admission to a hospital. A post-mortem examination revealed that she had ingested about 200 mg. of imipramine. It appears that the breakdown products of this drug are not traceable chemically in the various organs, as they are too complicated to assess.

In conclusion, it appears important to assess the reaction of these new anti-depressants on each individual patient and that, although in a majority of cases the results that we have obtained are satisfactory, the side-effects must be watched very closely, as they might be quite dangerous to a patient who is not under supervision.—I am, etc.,

Harrow-on-the-Hill, Middlesex. GLYN DAVIES.

Hazards of Iron-dextran

Sir,—The case presented by Drs. C. E. G. Robinson, D. N. Bell, and J. H. Sturdy (August 27, p. 648) relating to a possible association between malignant neoplasm and iron-dextran is of interest, but should be given no more significance than the facts warrant. The authors mention many of the points which make equivocal any aetiological association between "imferon" and the tumour they encountered. Dr. Sturdy has kindly allowed us to examine a section of their tumour, and we have little doubt that it is a liposarcoma. The small amount of iron demonstrated in it has not been proved to be derived from imferon, and is no more in amount than one might expect in any sarcoma as a result of haemorrhage. There is a sharp contrast between the amount of iron in this specimen and the heavy deposits associated with imferon-induced tumours in experimental animals. The lesion they describe in the deltoid region has not been proved to be a primary tumour. It is equally possible that it may be a metastasis from an occult primary. That tumours may metastasize to injection sites has been shown in published reports, a classic example being that of Ewing.[1] The case reported by Crowley and Still in the May 7 issue of the *B.M.J.*[2] may be another example.

Dr. Laurence V. Foye, jun., of the Veterans' Administration Hospital, San Francisco, has granted permission for us to present the essential clinical data (privately communicated) of a patient investigated by him.

A male patient, aged 45 years, has had severe, repeated gastro-intestinal haemorrhage since 1943. The cause for this bleeding has remained unexplained despite full investigation and two surgical abdominal explorations. Since 1945 he has received 71 units, each of 500 ml., of blood, thirty doses of "feojectin" intravenously, and, since 1957, 933 ml. of intramuscular imferon. The iron-dextran preparation was administered equally between two gluteal sites. The total weight of iron given from all of these sources was 67 grammes, of which 46.6 grammes were in the form of imferon. A biopsy was performed over the site of the intramuscular injections of the iron-dextran 46 days after the last administration. A heavy iron accumulation was found in the subcutaneous fat, but no evidence of neoplastic or precancerous change was seen.

The submission of this case is not an attempt to prove the non-carcinogenicity of iron-dextran. It does demonstrate that imferon may be administered repeatedly over a period of three years to a high total dose without tumour production within the period of observation.

We have been disturbed by the way in which the *B.M.J.* (March 12, p. 788, and August 27, p. 659) has interpreted the reported evidence relating to the possible carcinogenicity of iron-dextran. We feel that the approach has been biased, that the conclusions drawn have been based on rather tenuous evidence, and that critical scientific observation has been lacking in the application of the results of animal experimentation to humans. Neither the experimental findings of Richmond[3] and of Haddow and Horning,[4] nor the case reported by Dr. Robinson and his colleagues justify the abandonment of a therapeutic agent of the value of imferon.—We are, etc.,

T. H. CRAWFORD BARCLAY.
J. W. WHITTICK.

Allan Blair Memorial Cancer Clinic, Regina, Saskatchewan.

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[2] Crowley, J. D., and Still, W. J. S., *Brit. med. J.*, 1960, **1**, 1411.
[3] Richmond, H. G., ibid., 1959, **1**, 947.
[4] Haddow, A., and Horning, E. S., *J. Nat. Can. Inst.*, 1960, **24**, 109.

Masks or Silence

Sir,—Stimulated by recent correspondence arising from your leading article " Masks or Silence " (April 30, p. 1339) it seemed of interest to carry out some simple practical experiments. One of us, a surgeon and a known nasal carrier of *Staphylococcus aureus*, spoke for three minutes with a blood agar plate held three feet from the tip of the nose. There resulted approximately 14 colonies of *Staph. aureus*. As it is not unknown for surgeons to snort in exasperation, the same experiment was repeated. This time the surgeon snorted intermittently for three minutes. He did not speak. This resulted in approximately 27 colonies of *Staph. aureus*.

It seems reasonable to conclude from this that the wearing of efficient masks is necessary for all but the most silent and self-controlled surgeons. Clearly it becomes absolutely essential whenever the nasal staphylococcal reservoir is liable to be disturbed by violent exhalation.—We are, etc.,

E. G. Dolton.
C. H. L. Howells.

The Royal Hospital, Wolverhampton.

Myelocele Protection

Sir,—A myelocele or meningomyelocele is usually detected at or soon after birth. It is rarely treated by immediate surgery, for some spontaneously improve while others are associated with gross neurological involvement of legs, bowel, and bladder, and sometimes with an Arnold–Chiari malformation which may later lead to hydrocephalus. Hence it is expedient to treat these abnormalities conservatively for months or even years, and their daily redressing and continued protection present many problems. Tulle gras or dry dressings are the immediate covering, and these are guarded by

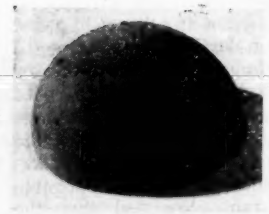

Fig. 1

Fig. 2

some semi-rigid cap which must be kept in place over the curved infant's back. It is the practice at Great Ormond Street to use a thick-walled rubber hemisphere (Fig. 1). This can be obtained in several sizes and is pierced by a few holes to allow some movement of air.

Recently a boy was brought to hospital for treatment of his meningomyelocele and his mother had grown tired of the conventional cap. She had found it difficult to hold in place except with yards of encircling crêpe bandages, and these, with the rubber cap itself, caused the skin of the back to become very hot and sweaty. She therefore used the device shown in Fig. 2. This is an ordinary kitchen sieve. It is light and allows easy circulation of air. By attaching it with tapes around the body from the handle and the two hooks on the periphery, the use of crêpe bandages can be avoided. A further improvement might be in the sawing off of the long handle (filing the sharp end so produced) and leaving a one-inch stump of metal only at this point for the attachment of a tape. These sieves can be obtained in various sizes from 2½ to 7 inches in diameter, and this patient had used several in turn as he grew, all with complete satisfaction.

This is brought to the attention of those who have the care of meningomyeloceles as an effective, cheap, and improved cover, which has the added advantage of being universally obtainable.—I am, etc.,

Hampstead N.W.3. Geoffrey Chamberlain.

Instructions with Infant Foods

Sir,—In my experience underfeeding is the commonest cause of difficulty in infant-feeding for which the G.P. is consulted. A great deal of parental anxiety and a considerable wastage of the G.P.'s valuable time could be avoided if the manufacturers of infant foods would supply more intelligent instructions with their products. Their present custom of suggesting a fixed food-intake for a child of a certain weight is iniquitous and grossly misleading.

Surely any table supplied should point out that a child's caloric requirements vary enormously, and that, if the infant seems not to be satisfied by the amount advised, it is perfectly safe to increase the feeds considerably. There are still too many doctors and nurses who regard over-feeding as dangerous and who are helping to perpetuate a problem which would never arise if mothers had suitable advice provided.—I am, etc.,

Belfast 14. S. E. Browne.

Mental Health Tribunals

Sir,—I am entirely in agreement with Dr. F. E. Graham-Bonnalie (July 30, p. 389) when he suggests that " old patients " constitute the bulk of a consultant's out-patient clinic. I am not so sure, however, that this is responsible for the staff of out-patient departments having " insufficient means of writing letters." If they were in the habit of writing repeated letters about " old patients " to the G.P. they would hardly have time to deal adequately with their clinical duties. In my own experience of ear, nose, and throat; surgical; medical; dermatological; ophthalmic; and orthopaedic out-patient clinics as well as those of own specialty—obstetrics and gynaecology—I would say that once the sufferer becomes an " old patient " he or she only too often passes into a sort of forgotten limbo of no return.

This state of affairs, in my opinion, is entirely the fault of the consultant in charge. Unless he instructs his registrar and house-surgeon that " old patients " who are not undergoing specific treatment must be returned to their G.P. they may only too easily become " chronic old patients." When I was a student at Charing Cross an obstetric officer who was more advanced in years than usual happened to be appointed. On discovering that his duties in out-patients consisted of " seeing the old patients " he at once took them seriously in hand. Having carefully scrutinized the out-patient records—frequently almost of book size—he questioned each one carefully as to their present state of health. Over and over again he concluded the interview by saying, " As you have no symptoms connected with this department I am discharging you back to your own G.P." Within a matter of weeks the " old patients " had decreased from about a hundred to a mere half-dozen.

This line of approach so impressed me at the time that I continued it as a consultant. I invariably instructed my

registrars and house-surgeons that I would not treat any "old patients" unless the G.P. requested me to do so having received my first report. In addition I invariably refused to treat patients referred for an opinion who proved to be "gynaecologically normal." Any additional investigations of a medical or surgical nature which might prove to be of value I would communicate to the G.P. After all, *he* had only requested a gynaecological opinion, and without his knowledge and approval I believed it to be improper on my part to involve the patient in a round of special investigations by other departments.

I entirely disagree with the hospital chairman who informed Dr. Graham-Bonnalie that "it had for many years been the custom and the duty of the hospital, once a patient had entered its doors, to continue to treat that patient until he was either better or dead." The duty of a consultant is surely to advise the G.P. who has sent the patient with regard to medical and surgical treatment. If the latter then requests the consultant to arrange for all treatment—medical and surgical—to be carried out in hospital that is quite another matter. But once the treatment agreed between G.P. and consultant has been completed, the patient must, in my opinion, be returned to the G.P. with a final letter. I freely admit that such a cut-and-dried routine may not be possible in some departments, but it certainly could be applied in the majority which treat surgical conditions.
—I am, etc.,

St. Austell, Cornwall. D. G. Wilson Clyne.

Nuclear Changes and Vitamin-B_{12} Deficiency

Sir,—Dr. P. C. Farrant discusses various theories of vitamin-B_{12} action in his report on "Buccal Mucosal Cells in Pernicious Anaemia" (June 4, p. 1694), admitting that "it is not clear why (deficiency of this vitamin) should cause enlargement of certain cells and their nuclei." Though it has the limitation of not yet having been demonstrated experimentally a theory has been proposed which may serve to explain Dr. Farrant's observations.

It is known that certain metalloporphyrins with two axes of asymmetry (a category into which vitamin B_{12} chemically fits) may act as polymer "clippers"—that is, they may interpose in a polymerization reaction to govern the formation of an appropriate sized macromolecule.[1] Chlorophyll, for example, is thus supposed to govern the degree of molecular condensation that forms carbohydrate; some hold this to be as important as (if not, indeed, an aspect of) chlorophyll's photosynthetic function. The alignment of the building-blocks of a nylon thread or sheet and the various vulcanizations applied to latex to procure the type of rubber desired are illustrations of optimally applied polymerization processes, and it is of interest that copper dihydromonovinyl-porphyrins or colbalt phthalocyanin sulphonate, an azoporphyrin, have been employed in rubber industry as such polymer clippers.

Stereochemical considerations in this field are highly involved and will not be detailed here. For present purposes it will suffice that the nucleic acids proper to a cell nucleus are nucleotide polymers whose molecular weight appears to be within a certain range whose median is about six million. For the optimal functioning of a cell nucleus, polymerization of either desoxyribo- or ribonucleotide must not extend above the upper limit of this range. Vitamin B_{12} is a unique porphyrin-like cobalt chelate co-ordinated with a single nucleotide which may be transferred to the terminus of the nucleic-acid polymer chain and thus accomplish "clipping" at a point of appropriate chain length. These considerations have been freely discussed among biochemists since the demonstration of B_{12} analogues containing different nucleoside bases,[2] but they seem not as yet to have been adapted to explain observations such as those made by Dr. Farrant. This adaptation is perfectly feasible. Nuclei of presumably B_{12}-deficient squamous cells are larger, and stain less *basophilically* intensively than do these nuclei from normal or remissive subjects. Dr. Farrant calls the latter relative "pyknosis." We would prefer to say that the nuclei of these cells in B_{12}-deficient subjects show relative "hypochromasia" due to diminished avidity for electropositive-colloid, "nuclear" dyes such as alum-haematoxylin, methyl green, or (in the case of the May–Grünwald–Giemsa stain used by Dr. Farrant) Azur II.[3] This itself is evidence of hyperpolymerization, just as in the converse case of nuclei of certain neoplastic cells, their *hyper*chromasia is due to relative nucleic-acid depolymerization.[4] The greater the degree of polymerization of nucleic acids, the less free phosphoryls there are available to bind such "basophilic" stains.

It may be considered impertinent to burden physicians with these chemical abstrusities, but they are justified by the importance and the topical nature of the observations by Dr. Farrant and those he cites and corroborates. With the emergence of designations of disease as "molecular," "chromosomal," and "depolymerization" in character, and with the knowledge that nucleic acids are helical, or spiral-chained, polymers it might be possible to explain the changes in axis-ratio and nuclear shape as contingent on the postulated change in polymer chain-length. It takes less force to distort a long spring than an equally constituted short one.

The general importance, however, of attempting an interpretation of these nuclear alterations on a macromolecular basis is that macromolecular dynamics have a more generalized range—they are not as "specific" or restricted as are micromolecular reactions. This is a philosophic point around which there is growing realization that those diseases which may once have been considered as "local" or "locally engendered" may actually be more "systematized" than once was believed. Whether there can exist any condition in which there has been severe nucleic-acid alteration without concommitant protein, carbohydrate "ground-substance," or even lipid polymerization disorganization is doubtful. Universal, relative degrees of depolymerization in the similar mucopolysaccharides of all tissue matrices has been suggested as unifying the nosology of the collagen-vascular diseases. And when depolymerization extends to intracellular nucleic acids, we are able to explain previously puzzling aspects of systemic manifestations of what had previously been considered as "local" malignant neoplastic disease.

Speculations around Dr. Farrant's observations are justified because of the elaboration of truisms, dignified to theory status, that jams the B_{12} literature. Obviously it is involved in nuclear synthesis, but what is not? That it is an enzyme, the prosthetic nucleus of an enzyme, a coenzyme, or that it participates in enzyme systems tells us very little since recent extension of "enzymology" includes almost anything found in the body in this category. Curiously enough, the probable metalloporphyrin nature of the "anti-pernicious anemia factors" was reported many years before the isolation of B_{12} on this enzyme basis[5] and, though in this instance a correct answer was obtained by faulty reasoning, there were certain solid premises on which to base this reasoning. Remission in pernicious anaemia was accompanied by a sharp rise in erythrocyte cholinesterase[6]; the latter was thought to be a "haem," porphyrin enzyme.[7] The premises were not logically connected in this instance.

We hope that those made in this paper will be better connected, as Dr. Farrant's observations deserve.—We are, etc.,

Division of Cancer Research, New York City Department of Health. Robert D. Barnard.

Harlem Hospital, New York City Department of Hospitals. Arthur C. Lewson.

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Phenothiazine Derivatives

Sir,—The article by Dr. Linford Rees on the uses of chlorpromazine and allied phenothiazine derivatives (August 13, p. 522) has prompted me to write concerning our experience with intramuscular "sparine" (promazine hydrochloride) as an adjunct to analgesia in obstetrics. During the past two years I have tried various combinations of pethidine, scopolamine, plus phenothiazine derivative. By using the latter, it was hoped to reduce the dosage of other drugs whilst maintaining or boosting their effect.

We have found the following dosages most suitable: A primigravida at two-fingers dilatation is given pethidine mg. 100, scopolamine gr. 1/150 (0.43 mg.), and promazine mg. 50, intramuscularly. Depending on the progress of labour, she may need a half "round of the cocktail" in four hours, or perhaps only "pethilorfan," mg. 100. A second full round is rarely needed. A multigravida in early labour will usually require only one full dose, or perhaps pethidine plus promazine only. Except in those cases specified below, analgesia plus amnesia has been "very good" or "excellent," the patients being very relaxed, with only a hazy memory of the labour ward. This statement is based on a combination of nursing sisters' impressions and the patients' remarks at post-natal visit.

Taking 75 consecutive cases, and excluding those who had very short hospital labours or caesarean sections, we can report on 30 multigravidae and 25 primigravidae who had planned analgesia. No undue delay was found in the establishing of respiration in the babies. Mucus-extraction or no treatment is reported for all except three. These cases were in white asphyxia; one was premature and subsequently proved to have an intracranial haemorrhage. The surviving two had foetal distress in the second stage of labour, presumably due to placental insufficiency.

Blood-pressure recordings in labour showed no significant fall, and no untoward reactions were noted—e.g., urticaria. Three low-forceps deliveries were blamed on the analgesia, the patients being too sleepy to bear down. We found it quite safe to allow the second stage to progress a little longer than usual before interfering. No changes in foetal pulse rates were observed which could be attributed to the drug. Four patients were very restless following the first dose of the mixture, but would probably have settled following a second injection. Three patients declared that the relief afforded was poor—one of these, a primipara, was 26 hours in a colicky type of labour, and had two full doses of mixtures plus 100 mg. of pethilorfan. The average duration of labour was 16 hours in the primigravidae and 8½ hours in the multigravidae. There was one post-partum haemorrhage following forceps delivery for persistent occipito-posterior.

The overall impression gained is of a quiet labour ward, with good relief of distress and no apparent increase in risk. I hope this formula may help in those practices where facilities for intravenous therapy are not easily available.—I am, etc.,

Robert F. O'Donoghue.

Bons Secours Maternity Hospital, Cork, Ireland.

Central Sterile Supply Departments

Sir,—After reading Dr. V. D. Allison's detailed analysis of his splendid organization (September 10, p. 772), I have thought it appropriate to comment upon his sixth paragraph. Central supply of sterile ward packs for minor operations, etc., was routine procedure at the London Hospital long before I served as a surgical dresser, which was in 1933, and very excellent was the system, which was also improved every year. It would be interesting to know if perhaps there has been a complete C.S.S.D. at the London Hospital during the post-war years. This would then have priority over the perfected organization in Belfast.—I am, etc.,

Department of Pathology, Torbay Hospital, Torquay. Peter Warren.

Our Hospitals

Sir,—Lord Taylor in his article on "Hospitals of the Future" (September 10, p. 752) suggested that the building materials and methods which were good enough for Wren are good enough for us. Would it be any less reasonable for an architect to claim that the methods prevailing in medicine at the time of Wren should be good enough for Lord Taylor? Progress in architecture, as in medicine, comes only from research and experiment. That failures occur in both fields as a result of such experiments does not invalidate the principle.—We are, etc.,

J. R. B. Green.
A. J. Noakes.

London N.14.

Caravans as Homes

Sir,—The paper by Dr. G. K. H. Hodgkin (September 17, p. 854) serves a useful purpose in illustrating a technique of assessing the health of a small community such as the occupants of a caravan site, but there is a real danger that the conclusions drawn from this survey of 31 children of 18 families living on a single poor site, with a turnover of families much more rapid than usual, may be used for highly misleading generalizations.

Apart from the very small size of the sample, we do not know if the site is a typical one. Even if it is, which from the description seems doubtful, the survey would not condemn caravan life, that should be judged on what it can and should be like, and not on what, in the stress of acute housing shortage and a great excess of demand over site supply, it very often is like. One might as well survey the health of families in one rather slummy block of flats and use that to condemn living in houses. However, I welcome Dr. Hodgkin's pointing out a gap which Sir Arton Wilson had to leave in his report, and would welcome further sample surveys of the same kind from other sites.

Future surveys should include some information on the size and quality of the caravans occupied. In some areas there are many shoddy medium-size holiday vans in use as permanent homes, and these are obviously very undesirable. The properly made 22-ft. (6.7-m.) residential models are a very different proposition, but even these have never been defended by this magazine as satisfactory for more than two people. They are vastly

better than the other accommodation (if any) available to the majority of the occupiers, but for bringing up children the larger caravans, up to 30 ft. (9.2 m.) long or larger, on which the manufacturers are now concentrating, are very much better. It is lamentable that just when the industry and the sites trade are offering these much superior caravan homes, the hire purchase restrictions limiting repayments to two years should make their purchase impossible for so many who have no other serious hope of a home of their own, and should force them into 18–22 ft. (5.4–6.7 m.) models built down to a price.—I am, etc.,

W. M. Whiteman,
Editor, *The Caravan*.

London W.C.1.

Survey of the Epilepsies

Sir,—Professor A. V. Neale in his letter (September 17, p. 856) rightly asks for a survey of fits occurring in small children as a corollary to the epilepsy study recently published by the College of General Practitioners. The Committee for Research in General Practice of the Medical Research Council is engaged in a long-term study of convulsions which it is hoped will answer amongst other questions some of those implied by his letter. In the current investigation, when a doctor is consulted for a convulsion in a person under 20 years of age, he records certain information about the patient and his family and about the family of a patient randomly selected as a control. The patients who have experienced a convulsion are to be followed for many years to determine their subsequent physical and mental development and their later experience of convulsions.

Would any general practitioner who would be interested to participate in this investigation get in touch with me?—I am, etc.,

R. E. Hope-Simpson,
Secretary, Medical Research Council Committee for Research in General Practice.

P.H.L.S. Epidemiological Research Unit,
86 Dyer Street, Cirencester.

POINTS FROM LETTERS

Crime and Sin

Dr. R. W. Cockshut (London, N.W.4) writes: Dr. R. H. Ahrenfeldt (August 13, p. 539) states that "a high ethical and moral standard . . . is not . . . dependent on the presence of a policeman." This may be so of standards, but is it true of behaviour, as, I think, Dr. Ahrenfeldt implies? There must be many of my contemporaries who remember the Liverpool police strike. I shall never forget the chaos which overtook the city in a few hours—i.e., as soon as the mob realized that there was no one to stop them looting the shops. It is fashionable to regard punishment and physical sanctions with distaste, but it is really no use creating an imaginary world, where some sort of humanist idealism will make us all good.

Osteoarthropathy and Gastric Carcinoma

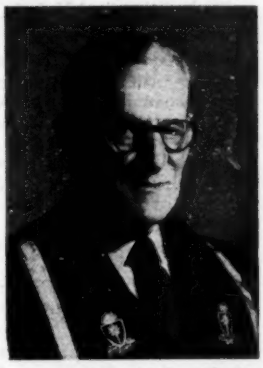
Dr. George X. Trimble (Memorial Hospital of Long Beach, California) writes: In the medical memorandum "Hypertrophic Osteoarthropathy Associated with Carcinoma of Stomach" (August 20, p. 581) a clinical correlation is reported, which apparently has hitherto been rarely described. In their discussion the authors indicate that they are unaware of any other reports of this association. Consequently, I wish to direct your attention to the medical memorandum "Arthropathy due to Gastric Carcinoma" which appeared at p. 1022 of the October 25, 1958, issue of your journal, and for which a claim of priority in publication was made. Subsequently (November 8, 1958, p. 1162) a correspondent told of some cases of his own, and cited an earlier publication on other similar cases.

Obituary

Sir ARTHUR GEMMELL, *M.C.*, M.D., F.R.C.S.Ed. F.R.C.O.G., Hon.M.M.S.A.

Sir Arthur Gemmell, whose health had been failing for many months, died at his home in Liverpool on September 24, aged 67. A Past-President of the Royal College of Obstetricians and Gynaecologists, he was formerly gynaecological and obstetric surgeon to the United Liverpool Hospitals and senior lecturer in obstetrics and gynaecology in the University of Liverpool.

Arthur Alexander Gemmell was born on November 2, 1892, the eldest son of the late Dr. John E. Gemmell, who himself was a well-known Liverpool gynaecologist. Arthur Gemmell's school was Uppingham, a fact of which he was always proud. From there he went to King's College, Cambridge, to study medicine. His undergraduate career was, however, interrupted by the first world war, and 1914 saw him a combatant in the Liverpool Scottish Regiment. After being wounded at Ypres in 1915 he served as adjutant in the Queen's Own Cameron Highlanders at Salonika. For his distinguished services there he was awarded the M.C. and also the Greek Military Cross. After that war, Arthur Gemmell was so enamoured of the life and discipline of the Forces that he was tempted to remain a professional soldier. Indeed, he did so for a short time, but disliked the necessary frequent changes of environment and ultimately returned to medicine.



Completing his clinical training at Liverpool University, he graduated M.B., B.Chir. (Cambridge) in 1922, and he subsequently proceeded M.D. of the same university. He was elected a Fellow of the Royal College of Surgeons of Edinburgh in 1924. Yet his love for the Army remained, and, as a Territorial, he commanded the Liverpool Scottish Regiment during the years 1923–7, being given the brevet of colonel. Moreover, his interest in military history never waned; until the time of his death, and except for medical literature and committee papers, he rarely read anything else. With this background it was not surprising that during the second world war he joined the R.A.M.C. Territorial unit of the University of Liverpool. This resulted in his spending many cold and dark nights on wayside railway stations, waiting for, receiving, and disposing of the wounded. These were the nights when he should have been resting from the daily and nightly demands made by his large obstetrical and gynaecological practice. For he followed in the footsteps of his father, and, between the years 1925 and 1927, secured a succession of appointments as honorary consultant at the Women's Hospital, the Liverpool Maternity Hospital, and the David Lewis Northern Hospital. He also served several other hospitals on Merseyside, but it was these three branches of the teaching hospital which remained his first concern until he retired from practice in 1957.

T. N. A. J. writes: Arthur Gemmell guarded the work and prestige of his hospitals as only he could. For his whole life, character, and work were marked by conscientious and informed attention to detail, by honesty of purpose, by selfless devotion, and by scrupulous concern for correct procedure. His eminence in the world of gynaecology, his

large practice, and his able writings were all founded primarily on these qualities. Every one of his patients, private or otherwise, received day-to-day personal attention from the chief himself; he never completed an operation without ensuring that a detailed record was made to his own dictation; he never sent an article to press without personally examining as well as entering every possible relevant reference in the literature. He administered with the same punctiliousness; he never chaired a committee without knowing every fact which might have a bearing on a problem to be discussed.

Ever precise, sometimes fussy, Arthur Gemmell was never obstructive to advance. Once he was satisfied with the evidence and arguments produced, he would do all in his power to promote progress in the practice of medicine and in the organization of medical services. He had much to do with such organization, because a man of his qualities could not avoid membership of committees. Indeed, it was usually not long before he became chairman or an officer of the committee. The medical boards and lay management committees of his own hospitals, the Liverpool Regional Hospital Board, the board of governors of the Royal Liverpool United Teaching Hospital, the Central Health Services Council, the Liverpool Cancer Control Organization, and various committees of the Royal College of Obstetricians and Gynaecologists, of the Ministry of Health, and of the British Medical Association all had reason to be grateful for his assiduous services rendered over many years. He was successively treasurer, vice-president, and trustee of the Liverpool Medical Institution. He was president of the North of England Obstetrical and Gynaecological Society in 1945, of the Section of Obstetrics and Gynaecology of the Royal Society of Medicine in 1957–8, and of the same Section at the Annual Meeting of the B.M.A. in Liverpool in 1950. He was one-time president of the University Club in Liverpool.

Arthur Gemmell's membership of the council and subcommittees of the Royal College of Obstetricians and Gynaecologists extended over a continuous period of 16 years. As honorary treasurer of the College he launched, in 1947, the first appeal for the moneys necessary for a building worthy of the College. It is fitting that he should have lived to see his early enthusiasm justified by the opening of the new College in Regent's Park by Her Majesty the Queen in July of this year. In 1952 Arthur Gemmell was elected President of the Royal College of Obstetricians and Gynaecologists, an office which he filled with distinction for three years. One of his duties at that time was to visit Australia and New Zealand, and while in Australia he officially opened the first College House of the Australian Dominion Council. As his responsibilities mounted, so did his distinctions. In Australia he gave the Arthur Wilson and Blackham Memorial lectures; in the United States of America he was made an honorary member of the American Gynecological Society, the American Gynecological Club, and the New Orleans Obstetrical and Gynecological Society; at home he was made an Honorary Fellow of the Edinburgh Obstetrical Society and admitted to an Honorary Mastership in Midwifery of the Society of Apothecaries.

At the zenith of his career, and at a time when he was most needful of her help, his wife developed a serious illness, which ultimately caused her death in 1957. This was a cruel blow, but with characteristic pertinacity, loyalty, and kindness he nursed and tended her through many years of invalidism. She would have no one else. This period of his life, spent mostly at the bedside of his wife or in the train between Liverpool and London, was a tremendous strain. But he bore it with unruffled exterior, and no one can say what he suffered behind his outward composure. For Arthur Gemmell was a man who disciplined himself never to show his feelings. This is one reason why he was such a first-class administrator and committee man. I do not remember him ever showing anger, although I have known many occasions when he would have been justified. Always he kept his head, tried to see the other standpoint, was scrupulously fair and honest, examined every situation according to facts rather than by impression and prejudice. And he never showed envy or malice. As a junior consultant in his team in four different hospitals I worked with Arthur Gemmell closely for many years, receiving from him constant loyalty and help. He was also at that time senior lecturer in obstetrics and gynaecology at the University of Liverpool and, by past tradition, had every right to expect to be the next professor. The occurrence of the vacancy, however, brought a change in the conditions of appointment so that his junior for many years superseded him as head of the university department. Had Arthur Gemmell been a lesser man, the situation would have been intolerable. In fact, by continuing to carry out the duties of senior lecturer with consideration and zest he, more than anyone else, ensured the smooth working of the university department during its formative years as a whole-time unit. Even though honours and distinctions were showered upon him, even when in 1955 he was knighted for his local and national services to medicine, he continued modestly and faithfully to work for the welfare of his hospitals and their teaching function.

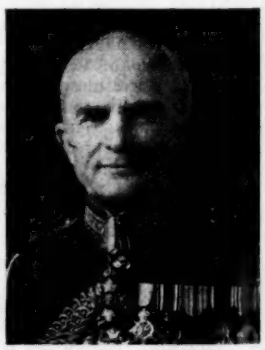
No matter how this man can be viewed, from the standpoint of patient, nurse, colleague, or friend, the picture is one of honest and selfless devotion to duty. Is this picture too cold? Not really: the warmth was there but he would have been embarrassed to show it.

Who's Who records that Arthur Gemmell's hobby was fishing. I do not believe that he fished more than ten times in all during the last 20 years of his life. He was too preoccupied in fulfilling his every commitment meticulously, almost relentlessly; such little time as was spent away from practice and committee matters was given over to his family. He was a man who burned away his life in service—service to his patients, his colleagues, his hospitals, his college, and his country. He leaves a son and two daughters, whose sorrow should be assuaged by pride in their father's courage, character, and achievements.

Sir VICTOR RICHARDSON, K.B.E., C.B., M.B. B.Ch., D.P.H.

Air Marshal Sir Victor Richardson, Director-General of Medical Services, Air Ministry, from 1938 to 1941, died at his home at Gerrards Cross on September 16. He was 76 years of age.

Albert Victor John Richardson was born on September 4, 1884, the second son of Lieutenant-Colonel Thomas Ferdinand Richardson, of the 5th Royal Irish Fusiliers. He studied medicine at Trinity College, Dublin, graduating M.B., B.Ch. in 1908, and he was Hudson Silver Medallist at the Adelaide Hospital, Dublin, in the same year. After qualification he joined the Royal Navy. In 1919, he transferred to the Royal Air Force, of which he eventually became Medical Director-General.



[*Hay Wrightson*

Sir Victor Richardson retired from the R.A.F. in 1941, and thereafter he became chief casualty services officer of the London Civil Defence Region. He served on the Council of the B.M.A. from 1943 to 1948 and was also a member of the Armed Forces Committee. Some years before that, while serving in the Middle East, he had been president of the Mesopotamia Branch of the B.M.A.

Sir Victor Richardson was twice married. His first wife died in 1929. He is survived by his second wife, daughter of William H. Hornibrook, F.R.C.S.I., and by the two daughters of his first marriage and the one daughter of his second.

Sir HAROLD WHITTINGHAM writes : Sir Victor Richardson spent 24 years of his life in the Royal Air Force, having previously been in the Royal Navy for nine years. He was one of the fifty medical officers selected for permanent commissions in the newly created R.A.F. in 1919; he had previously served for two years with the Royal Naval Air Service, and was appointed O.B.E. in 1919. He was commissioned in the R.A.F. in the then relatively high rank of wing commander—the D.M.S. was only an air commodore—and consequently Richardson held administrative posts throughout his R.A.F. career. First, he was principal medical officer of Middle East Command, after which he spent five years at the Air Ministry, then consecutively he was P.M.O. in India, Iraq, Coastal Area, Halton, Air Defences of Great Britain, and Bomber Commands. He was one of the leading pioneers in helping to build up the R.A.F. Medical Branch, and consequently was faced with many difficulties. However, he proved to be a very able administrator, and at the end of each of his tours as P.M.O. he had the satisfaction of seeing the medical establishments placed on a sound basis. In recognition of his fine work he was appointed C.B. in 1937.

His wide experience of these commands and staff in general made him highly fitted to become the Director of Medical Services at the Air Ministry in March, 1938. He was instrumental in gettting this post raised to that of Director-General, and he became the first D.G.M.S. of the R.A.F. in August, 1939, retiring in 1941. During his term of office as D.G.M.S. he had very heavy responsibilities in connexion with the great expansion of the R.A.F. at home and abroad prior to and in the first two years of the war. Richardson's foresight was exemplified by the building of stategically placed modern hospitals, especially at Ely and Wroughton, which played a very important part in dealing with casualties throughout the war. In addition, early in 1939 he was primarily responsible for setting up the Flying Personnel Research Committee, whose terms of reference were : "To advise the Secretary of State for Air on the medical aspects of all research affecting safety and efficiency in flying, including problems associated with the scientific selection and training of personnel, and measures designed to maintain their physiological and psychological efficiency." In connexion with this a Physiology Research Laboratory was established at Farnborough which did most valuable *ad hoc* research on problems of aircrew throughout the war to enable man to keep pace with the machine, and this has since grown into the world-renowned R.A.F. Institute of Aviation Medicine. Richardson was appointed Honorary Surgeon to the King in 1935 and was knighted three years later.

Sir Victor Richardson was small in stature but active as a young man and reasonably good at games. He was a highly principled disciplinarian, stern but just, dapper in dress whether in uniform or civilian clothes, and always made one aware of his rank. These characteristics gained him even early in his R.A.F. career the nickname of "King Dick." He was meticulous to a degree. Many who did not know him properly thought he was slow, but any apparent dilatoriness was due to time well spent in thinking matters over from all angles, after which he acted promptly and most efficiently. He possessed a good memory and it was amusing to watch him dictate a long minute or report. His paragraphs were usually lengthy and the sentences somewhat complicated, but, after dictating 3 or 4 paragraphs without any notes he would suddenly stop and say "Go back to para. 1 about the third line and delete so and so, and substitute something else." Paragraph 2 would probably be dealt with in a similar manner, then suddenly he would resume dictating where he left off in the middle of a sentence. His stern, somewhat pompous air gave the impression that he lacked a sense of humour, but he enjoyed a good joke and often one would catch a merry twinkle in his eye.

Those who were privileged to serve under "King Dick" were very sorry when his reign came to an end in 1941, and now they deeply mourn his final passing. To his wife and three daughters we extend our deep sympathy.

Air Vice-Marshal T. C. MORTON writes : The death of Air Marshal Sir Victor Richardson has deprived the few remaining "founder" members of the R.A.F. Medical Branch of one of their most senior retired colleagues. An excellent administrator, just to such a degree that he was harder with his personal friends than with others in case his personal feelings were misinterpreted, he was the soul of integrity. A pioneer in realizing the vital importance of physiology in its application to high-speed flying, he was largely instrumental in recruiting research physiologists from universities to come to the R.A.F. Laboratory at Farnborough. Here, as a result of their successful work, a feeling of mutual trust and co-operation arose between the doctors and the flying personnel which proved an inspiration to the other services. "King Dick," as he was universally referred to in his absence, was quiet and reserved in his manner, but behind this mask was a considerate, shrewd mind with a puckish sense of humour, which was, alas, kept well concealed and only revealed to his intimate friends.

The R.A.F. Medical Branch with the deaths this year of Sir James Kilpatrick, Sir Alan Rook, and now Sir Victor Richardson, each in his own way unique, has suffered a severe loss. They have left us, but their work will endure.

J. S. BAXTER, M.D., M.Sc., F.R.C.S.I.

Professor J. S. Baxter died at his home in Cardiff on September 11, aged 55. He was head of the department of anatomy in the University College of South Wales.

James Sinclair Baxter, though born in Dublin, was of Ulster extraction. The son of a distinguished lawyer, who simultaneously held professorships in Trinity College, Dublin, and in the Queen's University of Belfast, he had a distinguished undergraduate career in Belfast, where he graduated in science in 1926 and in medicine in 1929. As a student he was active in extra-curricular affairs, being president of the Students' Representative Council and a keen member of the O.T.C.

After qualification he held house appointments in the Royal Victoria Hospital, Belfast, and then joined the anatomy department of the Queen's University as a demonstrator, intending at first to train for a career in surgery. He was elected F.R.C.S.I. in 1932, and in that year also he obtained the degree of M.Sc. of Belfast. His success as a teacher and the influence of the late Professor Thomas Walmsley, however, directed his interests to scientific anatomy. In 1933 he was awarded a Rockefeller fellowship which took him to the United States. There, in Baltimore, at the department of embryology of the Carnegie Institution of Washington, and, under Dr. G. L. Streeter, he received the stimulus and training in embryology which determined him in his resolve to become an anatomist. There followed appointments successively to an assistant professorship of anatomy in McGill University, a university demonstratorship in Cambridge, and a readership in Bristol, where he obtained the degree of M.D. in 1946. He was elected to the chair in Cardiff in 1952. At the time of his death he was examiner in anatomy for the Universities of Cambridge and London. In 1934 he married Miss Mona Earles; she and a son, who is medically qualified, survive him.

Baxter's investigative work lay chiefly in the fields of embryology and histology. He made important contributions to our knowledge of the development of the mammalian urogenital system, and, in conjunction with Professor

J. M. Yoffey, to that of the histochemistry of the adrenal glands. His work was characterized by a scrupulous attention to the details of his techniques, and those who have seen his sections will never forget their perfection and beauty. His wide knowledge of human embryology stood him in good stead as editor of Frazer's *Manual of Embryology*.

Professor Baxter was very active in the affairs of the Anatomical Society. He had been a vice-president of the Society, had served for a long period on its council, and was a valued member of the editorial board of the *Journal of Anatomy*. His early death is a great loss to his college and department, to the subject he professed, and to his friends.—J. D. B.

MELANIE KLEIN

Mrs. Melanie Klein, who made outstanding contributions to the theory and practice of psycho-analysis, died in London on September 22, aged 78. Born in Vienna, she studied psycho-analysis in Berlin and elsewhere, and at the invitation of the late Dr. Ernest Jones she came to London in 1926, remaining there for the rest of her life.

We are indebted to Dr. D. W. WINNICOTT for the following appreciation: Mrs. Melanie Klein was not medically qualified; yet because of her work on the psychology of childhood and infancy she will be honoured among doctors, as she will be also among social workers and teachers and all who are concerned with the establishment of mental health.

Advances in knowledge spread rapidly, and are absorbed into accepted teaching, but it will be a long time before Melanie Klein's work is fully understood and its value assessed. It is certainly possible that in the course of time she will rank as the most important of those who have built on the work of Freud. Her work was indeed based on that of Freud, and it is an outstanding example of the development of Freud's theories, not depending in some important respect on a departure from his fundamental principles of psycho-analytic practice. Mrs. Klein's work, which followed on her psycho-analytic training in Berlin and Budapest, and which was done in Berlin until 1926, and from then on in London, was at first concerned with the analysis of children, although increasingly from the mid-'thirties she took for analysis adults, especially analysts who were in training or who were seeking further analysis after training. Working with children, she showed that the strict principles of psycho-analytic practice were applicable to the treatment of young children, even of children under 3 years of age.

Mrs. Klein's theoretical contributions have been immensely rich and have much influenced analysts and indeed all those who work with children, and it is from her work on primitive mechanisms and on the defences against anxiety that become organized in earliest infancy that has sprung the major part of modern research into the psychological roots of depression, paranoia, and schizophrenia. In particular, her concept of "the depressive position" linked constructive work with the sense of guilt that is inherent in health development, inherent because of the aggressive and destructive ideas, conscious and unconscious, that accompany loving.

Possessed of a fine intellect and a spacious personality, she enjoyed being a pioneer and a teacher. Above all she was a very fine practising analyst. She was able to go over in her mind at the end of a week's work every detail of every hour with each of her patients, each seen for an hour daily. Up to the end of her life she practised a full day and vigorously applied the psycho-analytic technique in the light of her rich understanding and her deep belief in the reality of the personal struggle in the unconscious of the individual. Had she not become ill she would certainly have enjoyed another decade of psycho-analytic work of the highest order.

Mrs. Klein had a sense of humour which made her a good friend. She knew humility, but she did not like to compromise, and this cost her some friendships. A severe blow that she suffered was the loss by death of Susan Isaacs, who had become a staunch supporter of her in her struggle to get her views accepted in the Psycho-Analytical Society and outside it. In the Society, the immense stimulus of her ideas will continue, and it must be left to the next generation of analysts to build further on such of her theoretic concepts that survive the test of time. Her main contributions were: *The Psycho-Analysis of Children* (1932), *Contributions to Psycho-Analysis* (1948), and *Developments in Psycho-Analysis* (1952).

Of her three children, one son died. Her daughter is Dr. Melitta Schmideberg, who has made a name for herself in the field of psycho-analysis applied to the study of the anti-social adolescent. Her younger son, Eric, lives and works in London, and with his wife Judy he provided her with the happiness of watching three grandchildren grow.

ALEXANDER SMITH, M.B., Ch.B., F.R.F.P.S.

Dr. Alexander Smith, physician superintendent of Stonehouse Hospital, Lanarkshire, died suddenly on September 3 while on holiday at Rothesay. He was 63 years of age.

Born on July 9, 1897, Alexander Smith was a native of Coatbridge, and spent almost all his professional life in Glasgow and Lanarkshire. He was educated at Gartskerrie Academy, Coatbridge Secondary School, and the University of Glasgow, where he graduated M.B., Ch.B. in 1921. Before this he had served as a surgeon sub-lieutenant in the R.N.V.R. during the later part of the first world war. After completing house appointments at Greenock and the Victoria Infirmary, Glasgow, he joined the medical staff of Robroyston Hospital, then the main hospital in Glasgow for the treatment of non-respiratory tuberculosis. Under the direction of the late James Taylor the modern treatment of surgical tuberculosis was being developed, and Smith became a recognized authority, contributing much of value to the literature on the subject. He also became deputy to the physician superintendent, and gained valuable experience in hospital administration.

In 1929 he was appointed physician superintendent of Stonehouse Hospital, a specialist hospital in Lanarkshire for the treatment of non-respiratory tuberculosis. There he continued not only to treat successfully this crippling disease but also to take an active part in advocating the reforms which have resulted, in his lifetime, in the almost complete eradication of this infection. During the second world war Stonehouse was much enlarged as an E.M.S. hospital, with general, surgical, and medical units, and additional specialist units were later added under the National Health Service, on the introduction of which Smith was appointed a consultant in orthopaedic surgery. He also undertook at this time the duties of physician superintendent at Cleland Hospital, where under his direction a modern geriatric unit has been established. In 1956 he was elected a Fellow of the Royal Faculty of Physicians and Surgeons of Glasgow.

Alex Smith was an outstanding clinician, widely read and informed on many aspects of medicine apart from his own specialty. He never spared himself; his nervous energy overcame physical exhaustion, and no one asked for his help in vain.

After settling at Stonehouse he took an interest in the local Division of the B.M.A., and in spite of his many commitments he found time to take an active part in its work, being chairman in 1946–7. For many years he was one of the Lanarkshire representatives in the Representative Body. An able and fluent speaker, he took a prominent part in the debates. At the inception of the National Health Service he was influential in bringing the consultant and specialist administration in the Western Region within the framework of the B.M.A. He was a past-chairman of the Scottish Central Consultants and Specialists Committee and a member of the Scottish Joint Committee and of the Central Consultants and Specialists Committee

(England). He was also a member of the Lanarkshire executive council and a representative of the hospital services on the local medical committee since its inception. Smith was a strong supporter of the freedom and independence of medicine, in the maintenance of the highest ethical standards, and above all in the essential unity of the profession. He had great integrity, outstanding intellectual capacity, and maintained throughout his busy life a catholic interest in English literature and the arts.

He was very fortunate in his family life, and in times of stress was sustained by the care and understanding of a devoted wife. His tragically sudden death was a great shock to all who knew him, since to the end he had been engaged in the full range of his many activities. In Lanarkshire his place will not easily be filled, and to those who have been privileged to know him well and to enjoy his friendship his memory will remain evergreen.

Dr. Smith is survived by his wife and three daughters, the eldest of whom is a medical student.—J. C. M.

R. S. ELVINS, L.R.C.P.&S.Ed.

Dr. R. S. Elvins, who practised for many years in Scarborough and was a Fellow of the British Medical Association, died suddenly at his home in Scarborough on August 5. He was 86 years of age.

Ralph Sedgly Elvins was born in Birmingham on December 17, 1873, and was educated at St. Edward's School and Birmingham University. Qualifying in 1897, he first served as ship surgeon and then became an assistant in a rural practice at Berkeley in Gloucestershire, where most of his visiting was done on horseback or bicycle. In 1901 he took a country practice at Tollerton, York, where he remained until 1921, when he went into practice at Scarborough. In 1935 he had a coronary thrombosis and had to retire from general practice.

Dr. Elvins was a keen and active member of the B.M.A. for over 60 years. He was vice-chairman of the York Division in 1913, and acting chairman during the whole of the first world war. He was also a member of the executive and ethical committees of the York Division for four years, and chairman of the York medical war committee for the same period. For thirty years he was a member of the North Riding local medical and panel committee, and its secretary for twenty years. He also served as a member of the North Riding insurance acts committee for fifteen years. In recognition of his long and outstanding services he was elected a Fellow of the B.M.A. in 1958 and presented with the framed certificate at a well-attended meeting of the Scarborough Division.

M. T. C. writes: Dr. Elvins was a shining example of the old-time family physician, popular and beloved, and he was a kind and loyal friend. To my knowledge there are many old patients in Tollerton and Scarborough who remember him with gratitude and affection to this day, for he was a wise and kind physician of the old school who always put the interest of the patient first, and would go to any length to help those who needed his assistance. He bore his many physical infirmities with the greatest patience and gallantry. He was a widower, and is survived by two daughters and a son.

H. N. STOKOE, B.M., B.Ch.

Dr. H. N. Stokoe, who practised at Finchley, died suddenly at his home there on September 17. He was 64 years of age.

Harold Nevill Stokoe was born on November 9, 1895. He received his medical education at Oxford and St. Thomas's Hospital, graduating B.M., B.Ch. in 1924. After holding a resident post at the Ilford Emergency Hospital he went into practice in Finchley, where he remained until his death. An honorary physician on the staff of the Finchley Memorial Hospital, he became a skilful anaesthetist, holding hospital appointments under the National Health Service.

Dr. Stokoe is survived by his widow and two sons, to whom deep sympathy is extended.

Drs. E. K. Gardner and J. D. Rochford write: It was with real sorrow that we heard of the sudden and untimely death of our friend and colleague, Nevill Stokoe, almost on the eve of retirement. A well-liked and much respected general practitioner, Dr. Stokoe was also a very able anaesthetist, and was attached to the Barnet group of hospitals. For more than ten years he served the hospitals, and was always so willing to give help for emergency work whenever he was asked to do so. His pleasant disposition endeared him to the staff of every theatre in which he worked.

Sir GORDON GORDON-TAYLOR, K.B.E., C.B. M.D., F.R.C.S.

The obituary of Sir Gordon Gordon-Taylor was published in the *Journal* of September 10 (p. 807).

Mr. Douglas Miller, Past-President of the Royal Australasian College of Surgeons, writes from Sydney, New South Wales: The news of Sir Gordon Gordon-Taylor's death has made sad the hearts of many Australian surgeons, and it is fitting that we should pay tribute to one who had come to be looked upon by us as the living patron saint of British surgery in this country. Gordon-Taylor made his first visit to Australia in 1934 as examiner in anatomy for the Primary Examination of the Royal College of Surgeons. I think that on this visit he first felt that liking for Australia and its people which developed fruitfully with subsequent visits and time spent here during the war. His affection for us—which he often expressed—was no empty sentiment but the spring of endless kindnesses and invaluable services. Knowing what he would do, it was indeed a privilege for us to be able to give to some departing embryo surgeon a letter recommending him to the interest of Gordon-Taylor. This was a high prize which we reserved only for such as were worthy of it, but over the years there were many of them. How good it was to think of these men arriving at the College on one of those days he set aside for receiving and helping them. It was a great experience to meet so great a man and find him so simple, and so genuinely interested in their problems and in giving that practical help which he could give so generously. How he would quiz them on all the men who had gone before, and how well he remembered them and their worth and their performance and with what a genuine interest. Nobody could assess what it has all meant to the surgery of this country: the help and advice in preparation for the Primary, the planning of later study for the Fellowship, and the help in obtaining the most suitable jobs. They did not underestimate the value of a recommendation from this doyen of British surgery. All this he gave to so many, and it started them on their careers as leaders and teachers of surgery in this country.

We liked his extraordinary genuineness, his candour of expression, keen criticism (especially for anything not British), his warm appreciation of good men and good work. We all loved him, and one of our first calls in London was to the College, to enjoy the chat, interspersed with some delicious scandal, the brisk walk through the streets, the carefully planned luncheon, in the old days at the Langham, and later at the Ritz, where he delighted to entertain. We knew that Christmas would bring the personally worded card, with the picture of his beloved Lord's, and it would have pride of place on our mantelpieces.

Very recently, by a happy inspiration of old friends and students in Australia and New Zealand, he was persuaded to sit for a portrait by Gunn. It was so characteristic of him to obtain a list of contributors and to write to each one a charming note—his last letter to most. A few weeks ago this beautiful work was presented to our College, where it will be proudly hung so that for generations it may remind

men of that lively, inspiring, enthusiastic personality, whose life was dedicated to surgery in a golden age, and they may learn of his wisdom, of his lovely surgical skill, and of a personal charm and elegance that lifted him high above the level of ordinary men.

Now he has gone and we have indeed lost a friend. "You are tough people," he often joked, but withal we sheltered very tender hearts for "G.T." There is none to take his place in our hearts, for who could be his understudy, or who his successor in those rare gifts of friendship which were something so peculiar to himself?

Medico-Legal

LABELLING OF POISONS

[From our Legal Correspondent]

Only two classes of person may retail poisons—namely, "authorized sellers of poisons" (i.e., qualified pharmacists, etc.), who may sell poisons included in both Parts of the Poisons List, and "listed persons," those whose names are on the local authority's list of persons allowed to sell Part II poisons. Part II of the Poisons List is generally restricted to articles in common use for purposes other than the treatment of human ailments, and which must be regulated separately if the public are to have adequate access to them. Under Part II are included, for instance, certain arsenical substances used in agriculture and certain metallic oxalates used in photography. There are stringent and detailed requirements made by statute and regulation concerning the manufacture, colouring, transport, storage, sale, and labelling of poisons.

An offence against the requirements concerning labelling was the subject of proceedings before the Woodbridge Magistrates on September 8 (*East Anglian Times*, September 9). Frederick H. Battle and William R. Battle, of 32 Beach Road, Rushmere, were fined £5 after pleading guilty to selling poison not labelled in the required manner. The poison sold was a bottle of disinfectant and the infringement was the failure to label it with the name and address of the vendor.

No person may sell or supply any poison included in either Part of the Poisons List unless its container bears a conspicuous label showing four items: First, the name of the poison; secondly, in the case of a preparation which contains poison as one of its ingredients, certain prescribed particulars as to the proportion of the poison to the total ingredients; thirdly, the word "Poison" or one of the other prescribed warnings (e.g., "Caution. This substance is caustic"); and fourthly, the name of the seller of the poison and the address of the premises on which it was sold. In addition, where a poison is contained in an embrocation, liniment, lotion, or liquid antiseptic, the container must be labelled, "For external use only"; and in the case of a liquid, other than a medicine, sold in a bottle of capacity not more than six pints (3.4 litres), it must be labelled "Not to be taken."

Owing to the scope of Part II of the Poisons List, these restrictions affect a number of people other than pharmacists. However, the first, second, and third of the labelling requirements do not apply to the sale or supply of certain specified poisons[2] to a manufacturer or wholesale dealer in poisons, so long as the outside of the package is labelled conspicuously with words indicating the dangerous properties of the poison. None of the labelling requirements apply to sales of poisons to be exported to purchasers outside the United Kingdom.

[1] Poisons List Order, 1958, S.I., 1958, No. 1015, Schedule 3, as amended by S.I., 1958, No. 2122.

[2] Poisons Rules, 1952, S.I., 1952, No. 2086, Schedule 2, as amended by S.I., 1958, No. 1016.

Vital Statistics

Diphtheria in Derby

A girl, aged 11, developed tonsillitis on August 19, 1960, and died on September 1 from myocarditis due to diphtheria. The diagnosis of diphtheria was made retrospectively, all swabs having been negative. On September 8 this girl's brother, aged 13, was admitted to hospital with diphtheria. Another brother, aged 7, was admitted as a carrier on the same day, and on the following day the mother and father were also found to be carriers and were admitted to hospital. A girl, aged 4, and a boy, aged 9, were admitted to hospital with diphtheria on September 10 and September 14 respectively. All the children concerned, whether cases or carriers, except one, attend the same school in Derby and live in adjacent streets. The bacillus isolated is of the intermedius type, and none of the cases or carriers have been immunized. We are indebted to Dr. V. N. Leyshon, medical officer of health of the county borough of Derby, for these particulars.

Certifying the Cause of Stillbirths

Under the Population (Statistics) Act, 1960, doctors and midwives in England and Wales will be required to make a statement of the cause of death of every stillborn child on or after October 1, 1960. A similar provision has existed in Scotland since 1938. The object is to provide a regular series of statistics on the causes of stillbirths which together with other information obtained at the registration of a birth should help in the study of perinatal mortality. Previously in England and Wales this study has been restricted to the causes of death of live-born infants. From October 1 the present certificate of stillbirth will become obsolete and a new form of certificate will come into use which in addition to the declaration that the child was not born alive will provide for a statement of the cause of death "to the best of the knowledge and belief" of the person signing the certificate. The estimated duration of the mother's pregnancy and the weight of the foetus, if known, should also be given on the certificate. Books of certificates will be obtainable from local registrars of births and deaths, and the Registrar-General is to circularize doctors and midwives about details of the new procedure.

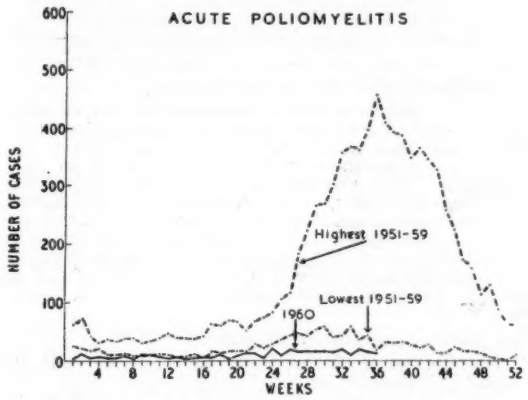
Infectious Diseases

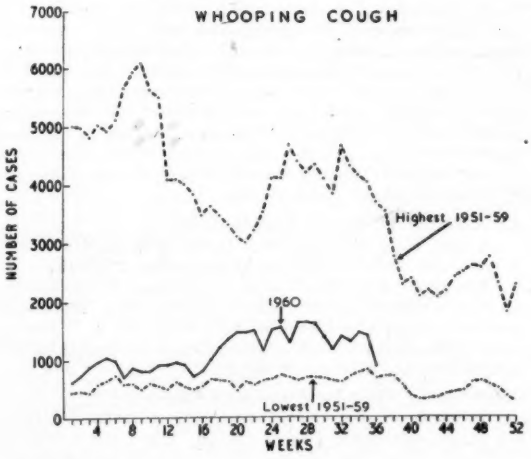
Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

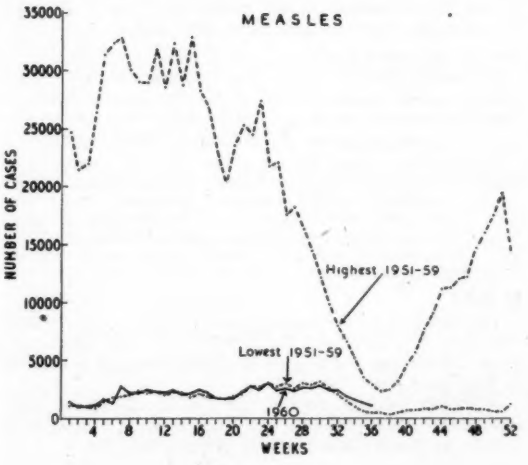
	Week Ending Sept. 10	Week Ending Sept. 17
Acute poliomyelitis		
London	1	7
Islington	0	3
Dysentery		
Lancashire	71	45
Liverpool C.B.	22	18
Yorkshire West Riding	46	56
Leeds C.B.	14	22
Glasgow	111	144
Food poisoning		
London	29	26
Hampshire	8	22
Southampton C.B.	7	17
Lancashire	24	28
Diphtheria		
Derbyshire	1	2
Derby C.B.	1	2

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 10** (No. 36) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..			0	0		6	6	1	0	
Dysentery ..	374	47	142	16	3	414	47	181	5	
Encephalitis, acute	2	0		0		6	0		0	
Enteric fever:										
Typhoid ..	6	0	0	0		9	3	0	2	
Paratyphoid ..	6	1	0	0		20	1	1(B)	0	
Food-poisoning ..	215	29	30	4		291	34	18	2	
Infective enteritis or diarrhoea under 2 years				19	38				23	
Measles*	1,156	40	25	2	8	848	32	22	13	
Meningococcal infection	14	3	10	0	1	6	1	14	3	
Ophthalmia neonatorum	20	4	4	0	1	19	1	4	1	
Pneumonia† ..	122	3	92	3	1	107	6	96	1	
Poliomyelitis, acute:										
Paralytic ..	5	1	0	} 0	2	{ 26	4	0	} 1	
Non-paralytic ..	7	0	0			{ 12	2	4		
Puerperal fever§ ..	176	30	8	1		220	28	17	0	
Scarlet fever ..	166	15	35	15	11	303	16	62	27	
Tuberculosis:										
Respiratory ..	357	55	48	11		424	52	58	15	
Non-respiratory	47	5	10	2		54	6	17	3	
Whooping-cough	1,376	120	141	4	13	695	50	176	9	

DEATHS	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	1	1		1		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	0	0	0	5	0	1	0	0
Influenza	5	0	0	0	0	4	1	0	0	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia ..	353	17	10	9	1	326	26	6	5	5
Poliomyelitis, acute	1	1		0	0	5	2		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	} 56	{ 3	2	0	0	} 56	{ 4	5	0	0
Non-respiratory		{ 0	0	0	1		{ 1	0	0	0
Whooping-cough	1	0	0	0	0	2	0	0	0	0
Deaths 0–1 year ..	276	34	30	3	6	274	20	17	8	12
Deaths (excluding stillbirths) ..	8,349	665	507	88	139	7,947	635	430	103	134
LIVE BIRTHS ..	14,666	1284	953	249	426	13,811	1216	938	259	370
STILLBIRTHS ..	272	22	23			309	33	20		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Secretary-General, World Medical Association

At its meeting in Berlin last week the General Assembly appointed Dr. HEINZ LORD as Secretary-General of the World Medical Association in succession to Dr. LOUIS H. BAUER. Dr. Lord is 43 years of age, and took his medical degree at the University of Hamburg, having studied also in Zurich and Berlin. Dr. Lord is a surgeon, and moved to the United States of America in 1954. He has practised surgery in the State of Ohio for the past three years. Dr. Lord is a member of the American Medical Association and of the German Urological Society.

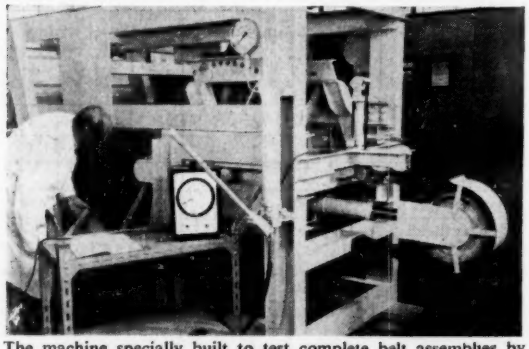
Russian as W.H.O. Working Language

W.H.O.'s Regional Committee for Europe has recommended that Russian should join English and French as a working language of the Regional Organization for Europe. The U.S.S.R. has pointed out that Russian is the mother tongue of more than half of all medical workers in the European Region, and the first foreign language of medical workers in Eastern European countries. The final decision rests with the W.H.O. Executive Board and the World Health Assembly.

Car Safety Belts

A British Standards Institution specification for car safety belts and harnesses has recently been published (B.S. 3254). Samples of belts which are to carry the kite-mark undergo a series of stringent tests at the B.S.I.'s Hemel Hempstead centre.

The main tests carried out are to prove, under strain, that the webbing used will not stretch unduly, that the buckle when



The machine specially built to test complete belt assemblies by applying a 4,000-lb. load.

fastened will not give way but will be of the quick-release type, and that the whole seat belt, when fitted to a dummy figure, will successfully withstand a load of 4,000 lb. without showing signs of damage. This figure represents accident conditions in which a load is imposed of twenty times the weight of a 14-stone man.

L.C.C. on Smoking

The London County Council has prepared a leaflet on smoking and lung cancer which it has distributed to London doctors, welfare centres, and borough libraries. The leaflet states: "In 1933 in London 7,093 people died of cancer, and 644 of these died of lung cancer. Only 25 years later, in 1958, in our own county 7,981 people died of cancer, 2,050 of them of lung cancer." The pamphlet goes on to say: "Doctors nowadays accept that cancer of the lung is closely linked with tobacco smoking, especially heavy cigarette smoking." The L.C.C. state that the local medical committee and the M.O.H.s of the Metropolitan boroughs were consulted in the preparation of the leaflet, and that it incorporates their views.

Medical Insurance Agency

The thirty-second annual meeting of the Agency was held on September 15 at B.M.A. House. At this meeting the chairman, Dr. JAMES FENTON, who had served on the committee for 20 years and as chairman for 13, and Sir HENRY SOUTTAR, who had served for over 33 years, retired from membership of the committee of management. Presentations and tributes to the work and years of distinguished service they had rendered to the Agency were made at a reception held at the close of the meeting. During the year the Agency also suffered great loss through the death of Sir HENRY TIDY, who had been a much-respected member and served on the committee for 14 years.

Mr. R. W. RAVEN, a member of the committee of management for the past 14 years, was elected chairman to succeed Dr. Fenton, and three new committee members were elected: Professor THOMAS ANDERSON, Sir JOHN RICHARDSON, and Dr. D. P. STEVENSON. It was reported that business in all departments of the Agency had reached new high levels during 1959, and the special Personal Accident Scheme for members of the B.M.A. had proved a great success. The medical charities will benefit by over £38,000 from the donations allocated from the year's surplus. The committee of management paid tribute to the work of the executive board, the general manager, Mr. A. N. DIXON, and his staff.

Hospital Appointments in France

The Collège de Médecine des Hôpitaux de Paris has made arrangements whereby young doctors from other countries can obtain junior hospital appointments in Paris hospitals. The posts can be held for between one and three years. The salaries and allowances paid are those given to French "internes." Candidates must have passed their qualifying examination in medicine and had two or three years' experience. They must also have a good knowledge of French. Applications are now being invited for appointments for the academic years beginning October 1, 1961. Further details and application forms can be obtained from the Scientific Office, French Embassy, 22 Wilton Crescent, London S.W.1.

King Edward Medical College, Lahore

The president of Pakistan, Field-Marshal MOHAMMAD AYUB KHAN, will inaugurate the centenary celebrations of the King Edward Medical College, Lahore, on November 16. The celebrations, which will last five days, include a centenary oration by Lieutenant-Colonel S. M. K. MALLICK, dean of the medical faculty, University of the Punjab, and a reception by the Minister of Health.

More Family Planning Association Clinics

During the twelve months up to the end of June, 1960, the F.P.A. established 27 new clinics. This made a total of 319 clinics, four-fifths of which were housed in local authority or regional hospital board premises. (*Family Planning Association : 29th Annual Report, 1959–60.*)

Unicef Christmas Cards

Christmas cards of the United Nation's Children's Fund will be on sale from October 3 at Keysign House, Baldeston Street, London W.1 (opposite Selfridges). Postal inquiries should be sent to Unicef, 14–15 Stratford Place, London W.1.

As examples of what can be bought with the money contributed, 1d. (United Kingdom sterling) can buy enough B.C.G. vaccine to protect a child against tuberculosis, 4d. enough penicillin to cure one case of yaws, 7s. 2d. enough sulphone tablets to treat one case of leprosy for three years or provide 17 children with a daily glass of milk for a month, and £8 4s. 3d. will buy a complete midwifery kit.

In Brief

The Hungarian Government has issued an order making treatment for tuberculosis compulsory. The death rate from this disease in Hungary has fallen from 14 per 10,000 in 1938 to 3.1 in 1958.

A mobile information unit for use in cancer education has been handed over to the Manchester Committee on Cancer by Rotary International, District No. 105.

COMING EVENTS

Birmingham and Midland Medical Art Society.—Exhibition at 36 Harborne Road, Edgbaston, Birmingham 15, October 4 and 5, 6 p.m. to 10 p.m. Some of the exhibits are for sale.

Medical Protection Society.—Annual general meeting, 3 p.m. on October 5, at 50 Hallam Street, London W.1.

Medical Faculty, Leeds University.—Sir Robert S. Aitken will deliver the inaugural address at 3 p.m. on October 14 on "Medicine To-day and To-morrow."

Empire Rheumatism Council Symposium.—"Immunology in the Rheumatic Diseases," October 28, at the Apothecaries Hall, London.

Course in Genetics, Statistics, and Radio-Isotopes.—October 31 to November 2, at Institute of Basic Medical Sciences, Royal College of Surgeons of England (Holborn 3474).

Festival International Permanent du Film Medico-Chirurgical et Scientifique.—Faculty of Medicine, Paris, November. Organized in collaboration with *Gazette Médicale de France* by Association Nationale des Médicins Cinéastes et des Cinéastes Scientifiques de France. Details from the A.N.M.C.C.S.F., 23 Bd. de Latour-Maubourg, Paris 7.

Chest and Heart Association.—Symposium on Asthma, under the chairmanship of Professor John Crofton, in Edinburgh, November 2, 4.30–7 p.m. Tickets (one guinea) from the Chest and Heart Association, 65 Castle Street, Edinburgh 2.

Fourth International Congress of Neuropathology.—Munich, September 4–8, 1961. The programme will consist of (*a*) general sessions and (*b*) three symposia on tissue culture, histochemistry, and electron microscopy, with reference to the nervous system. Details from General Secretary of Congress, Professor H. Jacob, Universitäts-nervenklinik, 8 Ortenbergstrasse, Marburg/Lahn, Germany. Intending contributors from United Kingdom, who have not already done so, should forward titles without delay to Professor C. E. Lumsden, Secretary of the British Committee, School of Medicine, Leeds 2.

NEW ISSUES

JOURNAL OF NEUROLOGY, NEUROSURGERY, AND PSYCHIATRY

Relationships Between British and Russian Medicine and Neurology, and the Role of the National Hospital, Queen Square, London, in the Development of Russian Neuropathology. N. I. Grashchenkov.
Baillarger and Jackson: The Principle of Baillarger-Jackson in Aphasia. Th. Alajouanine.
Tumour Cells in the Cerebrospinal Fluid. Vincent Marks and David Marrack.
Improvement in Cutaneous Sensibility Associated with Relief of Pain. P. W. Nathan.
A Case of Juvenile Gaucher's Disease with Intraneuronal Lipid Storage. A. F. J. Maloney and J. N. Cumings.
Effects of Flexion-extension Movements of the Head and Spine upon the Spinal Cord and Nerve Roots. J. D. Reid.
Spinal Withdrawal Reflexes in the Human Lower Limbs. K. E. Hagbarth.
The Occasional "Independence" of Dyslexia and Dysgraphia from Dysphasia. T. Casey and G. Ettlinger.
Angiographic Finding of an Aneurysm and Arteriovenous Malformation in the Posterior Cranial Fossa in a Case of Subarachnoid Haemorrhage. R. Myles Gibson and A. N. da Rocha Melo.
A Case of Dermal Sinus of the Nose with Frontal Suppuration. J. G. Hamilton.
The Prognostic Significance of Depersonalization in Depressive Illnesses Treated with Electroconvulsive Therapy. Brian Ackner and Q. A. F. R. Grant. Statistical Appendix by A. E. Maxwell.
A Case of Cysticercosis, Temporal Lobe Epilepsy, and Transvestism. Brian M. Davies and F. S. Morgenstern.
Parageusia Following Bell's Palsy: A Result of Faulty Re-innervation. Geoffrey Rushworth.
Alterations of Size Constancy Associated with Brain Lesions in Man. Maria Wyke.
The Babinski Sign. Marek Szapiro.
Book Reviews.

Volume 23, No. 3. (Quarterly; £3 annually.)

OPHTHALMIC LITERATURE

Volume 13, No. 5, 1959, and Volume 14, No. 1, 1960. (Quarterly; £4 4s. annually. Combined with *British Journal of Ophthalmology*, £9.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 3

Marlborough Day Hospital.—8.15 p.m., Dr. G. M. Carstairs: Recent Trends in American Psychiatry.

Tuesday, October 4

Leeds Neurological Sciences Colloquium, 1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. Macdonald Critchley: Broca's Contribution to Aphasia—Reviewed a Century Later.
West End Hospital for Neurology and Neurosurgery.—5.30 p.m., Mr. Ian McCaul: Involuntary Movement.

Wednesday, October 5

Anglo-American Medical Society.—At Cambridge University Department of Chemistry, Lensfield Road, 8 for 8.30 p.m., Dr. Paul Wood: Recent Advances in Cardiology.
Fountain Hospital.—5.30 p.m. (1) Dr. M. J. Craft: Problems Arising from a 90% Annual Discharge Rate from a Hospital for the Subnormal. (2) Dr. M. Susser and Dr. Z. Stein: Cultural Syndrome of Mental Retardation. A discussion will follow.
Institute of Dermatology.—5.30 p.m., Dr. H. Haber: Histology of Normal Skin.
Institute of Diseases of the Chest.—5 p.m., Dr. J. R. Bignall: Some Problems of Lung Cancer.
Institute of Urology.—4.30 for 5 p.m., Mr. F. R. Kilpatrick: Injuries of the Urinary Tract.
●Leeds University.—At General Infirmary at Leeds, (1) 5 p.m., Miss Ursula M. Lister: Endometriosis. (2) 6 p.m., Sir Andrew Claye: Dyspareunia.
Postgraduate Medical School.—2 p.m., Professor G. M. Bull: Place of Chemical Pathology in Medicine.

Thursday, October 6

St. George's Hospital Medical School.—5 p.m., Dr. Desmond Curran: postgraduate demonstration in psychiatry.
Society for the Advancement of Anaesthesia in Dentistry.—At Royal Society of Medicine, 7.30 p.m., Sir Robert Macintosh: Two Months in China
●West London Medico-Chirurgical Society.—At Rembrandt Hotel, S.W., 7.30 for 8 p.m., Presidential Address by Mr. Harvey Jackson: Pathways to the Brain.

Friday, October 7

●Institute of Dermatology.—5.30 p.m., Dr. I. A. Magnus: clinical demonstration.
Institute of Diseases of the Chest.—5 p.m., Dr. J. Smart: clinical demonstration.
Liverpool Society of Anaesthetists.—At Liverpool Medical Institution, 8 p.m., Dr. H. J. V. Morton: Clinical Experiments Galore.
Medical Electronics Discussion Group.—At Institution of Electrical Engineers, Savoy Place, London W.C., 5.30 for 6 p.m., discussion to be opened by Dr. O. C. J. Lippold and Dr. D. R. Wilkie: Nerve Endings.
Postgraduate Medical School.—(1) 10 a.m., Professor L. N. Pyrah: Some Aspects of Renal Calculi. (2) 4 p.m., Professor G. M. Bull: Regulation of Water and Salt Excretion.
Royal Society of Health.—At Assembly Room, Town Hall, Birkenhead, 10.30 a.m., Dr. B. K. Ellenbogen: Medical and Social Aspects of Old Age; Mr. F. Roberts, F.Inst.P.C.: Hygienic Refuse Disposal.
Whipps Cross Hospital Medical Society.—8.30 p.m., Mr. Geoffrey Flavell: Treatment of Hiatus Hernia (with short colour film).

Sunday, October 9

Dental and Medical Society for the Study of Hypnosis: Midlands Branch.—At Birmingham Medical Institute, 4 for 5 p.m., joint meeting of all branches. Film and Brains Trust.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Higgie.—On September 21, 1960, at St. Ives, Ellesmere, Salop, to Dr. Jean (formerly Lowick) and Dr. C. B. Higgie, a son—Robert.

MARRIAGES

Kohler—Pate.—On September 15, 1960, at Bonkyl Church, Berwickshire, Hamish MacGregor Kohler, M.B., Ch.B., to Georgina Pate, R.G.N., S.C.M.

DEATHS

Arthur.—On September 6, 1960, at King Edward Memorial Hospital, Ealing, London W., George Arthur, M.B., Ch.B., of 2 St. Stephen's Avenue, Ealing, aged 81.
Belcher.—On September 1, 1960, James Arthur Belcher, M.D., of 7 Homesdale Road, Petts Wood, Kent, formerly of Wolverhampton, Staffs; Herne Hill, London S.E.; and Knockholt, Kent; aged 90.
Bourke.—On September 4, 1960, in hospital, John Bourke, M.B., B.Ch., of 315 Heywood Road, Prestwich, Manchester.
Clifford.—On September 7, 1960, Harold Charles Clifford, L.M.S.S.A., of East Meon, Hants.
Coles.—On September 1, 1960, at Coombe Cottage, Fittleworth, Sussex, William Edward Kyte Coles, M.D., Lieutenant-Colonel, R.A.M.C., retired, aged 69.
Cruickshank.—On September 1, 1960, at Addenbrooke's Hospital, Cambridge, Mary Walker Cruickshank, M.B., Ch.B., of College of St. Mark, Audley End, Saffron Walden, Essex.
Foster.—On September 3, 1960, at St. Maurice House, Plympton, Devon, Raymond Leslie Vachell Foster, M.B., B.Ch., Lieutenant-Colonel, R.A.M.C., retired, aged 86.
Lewis.—On August 30, 1960, Arthur Picton Rossiter Lewis, M.B., B.S., D.P.M., D.P.H.
Salpe.—On August 27, 1960, Roland Gould Salpe, M.R.C.S., L.R.C.P., of 389 Harrogate Road, Leeds, Yorks, aged 46.
Tait.—On September 3, 1960, James Melrose Tait, O.B.E., M.D., of Sutton, Surrey.
Whitfield.—On August 28, 1960, John David Whitfield, M.B., Ch.B., D.P.H., of 86 Turnpike Lane, London N., formerly of Amoy, China, and Edinburgh, aged 68.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Swimming Under Water

Q.—*A healthy young man with apparently healthy ears feels momentarily nauseated and giddy, together with a numbness of the anterior part of the tongue, after swimming under water. The symptoms can be prevented by wearing cotton-wool in the ears. What is the mechanism of this syndrome ?*

A.—Nausea and giddiness may be produced by caloric stimulation with cold water as in the caloric test of labyrinthine function. This is due to the movement of the labyrinthine fluids caused by the temperature changes, and it is conceivable that this would happen with a person with an intact tympanic membrane when swimming under water in very cold water. It is very difficult to explain the numbness in the tongue, which must presumably be due to stimulation of the chorda tympani nerve. One would not expect this effect with a healthy ear, and this particular symptom would suggest that there might be some perforation.

Anti-catarrh Vaccine

Q.—*What is the prophylactic value of anti-catarrh vaccine ?*

A.—It is assumed that this question refers to the use of stock "anti-catarrh" vaccines for the prevention of colds. G. S. Wilson and A. A. Miles' should be referred to for a full review of this subject. Having pointed out (1) that the causative organism, a virus, is not included in such vaccines, and (2) that even resistance to secondary infection is not to be expected, since the bacterial species in the vaccine are "antigenically highly heterogeneous, and only a few arbitrarily selected types of each species can be included," they go on to review the published findings of controlled trials. In nine such studies, some including hundreds of vaccinated persons compared with unvaccinated controls, there was no evidence that vaccination diminished the frequency of colds, and very little that it diminished their severity.

J. Morrison Ritchie[2] claims that the frequency and severity of colds can be substantially reduced by autogenous vaccines. These were prepared by simply washing off the whole primary growth obtained from throat and nasal swabs and saliva (this gave the "best" growths); they must therefore have consisted very largely of saprophytic bacteria. The aim at first was to administer a dose of this vaccine every week throughout the winter: considerations of convenience compelled a reduction of the course to eight doses in many cases. Even this is a laborious proceeding: its effect is incomprehensible except as a purely non-specific stimulus to the reticulo-endothelial system, and it has not yet, so far as we are aware, been confirmed by other workers.

References

1 Wilson, G. S., and Miles, A. A., *Principles of Bacteriology and Immunity*, 1955, 4th ed., vol 2. Arnold, London.
2 Morrison Ritchie, J., *Lancet*, 1958, **1**, 615.

Streptomycin in Acute Pancreatitis

Q.—*What is the value of streptomycin in the treatment of acute pancreatitis ?*

A.—Streptomycin is of limited value in the treatment of acute pancreatitis. Its only value would appear to be in preventing secondary infection in necrotic pancreatic tissues, but it would seem to have no specific action on the pancreatitis itself. There is no specific treatment for acute pancreatitis save the administration of morphine to control pain, the use of atropine and nitrites as antispasmodics, and liberal parenteral fluids. Some authorities recommend plasma, 250–500 ml. intravenously, for this condition. If ileus develops foods and fluids should be withheld by mouth and continuous gastric suction applied. Surgical intervention is almost always required to confirm the diagnosis and to exclude associated disease such as biliary tract disease and peptic ulceration.

Ultra-violet Ray Therapy

Q.—*Are there now any medical indications for ultra-violet ray therapy in this country ?*

A.—Ultra-violet radiations are used extensively in dermatology. Wide areas of skin are irradiated for psoriasis and for acne and the rays are given by local application for indolent ulcers.

NOTES AND COMMENTS

Isoprenaline in Chronic Bronchitis.—Dr. B. Gandevia (Melbourne, Australia) writes: I should be most grateful if your expert would quote the evidence for his statement ("Any Questions ?" May 7, p. 1443) that the effect of the adrenaline–ephedrine groups of drugs "is greatest at the first administration and falls off with frequently repeated administration," irrespective of the route. I am aware of objective support for this only in so far as oral ephedrine is concerned, and I would also agree with the statement if by "frequently" he means hourly or so. Tests of ventilatory capacity in relation to bronchodilator therapy do not otherwise, in my opinion, support his contention. In fact, there is evidence[1] for either an increasing or a decreasing response to repeated administrations of a bronchodilator drug according to the initial severity of the reversible obstruction. However, these responses are independent of "pharmacological tolerance," to which your expert is probably referring, and he may also consider that the administrations were not "frequently" enough repeated.

These comments in no way invalidate the admirable practical advice which your expert gives. I am most interested in the mode of action of bronchodilator drugs, and his answer implies that I may have overlooked some important published data.

Reference

1 Hume, K. M., and Gandevia, B., *Thorax*, 1957, **12**, 276.

Our Expert replies: I think that Dr. Gandevia is correct in his statement that quantitative evidence is available for my statement about the diminution in the effectiveness of antispasmodic drugs in asthma only in relation to ephedrine. In relation to isoprenaline and adrenaline it is based only upon clinical observations, and I would agree with his implications that this phenomenon is more evident with ephedrine than with the other two drugs. My reference to this point was designed to discourage the prescribing of antispasmodics of this type in a schedule of regularly repeated daily doses. I am, of course, aware of the interesting observations of Drs. Hume and Gandevia, which undoubtedly account for some of the apparent variations in effectiveness of antispasmodic drugs on repeated administration to patients with reversible airway obstruction.

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